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Review Article

Probiotics and their benefits in pediatric patients

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ABSTRACT

Respiratory tract diseases are among the most common infections in childhood and adolescence. In recent years, probiotics have emerged as a promising prophylactic and curative alternative for various digestive, mental and respiratory pathologies. This is attributed to the significant influence that the intestinal microbiota exerts on the immune system. Multiple studies indicate that an impact on the microbiota due to external or internal factors leads to an alteration in the immune system. Among their current uses, they are used for the prevention and treatment of respiratory diseases in children. The studies analyzed show that Lactobacillus casei shows better results in preventing upper respiratory diseases than other probiotics, whether combined or alone. However, the duration of administration is unknown. New advances increasingly point to the positive effect that probiotics show in children, especially those who present repetitive viral or bacterial symptoms. Different investigations open doors and excellent results have been obtained with the use of probiotics.

Keywords: Microbiota, Probiotics, Respiratory tract diseases

INTRODUCTION

Respiratory tract infections (RTIs) are the most common conditions in pediatric patients. Globally, approximately 20% of deaths in children under 5 years of age are secondary to RTIs, with pneumonia being the most prevalent. Studies indicate that 25% of infants and 6% of children under 6 years of age experience respiratory tract infections. Respiratory tract infections are one of the leading causes of antibiotic use, which in many cases is unnecessary and causes high rates of bacterial resistance. Probiotics are small microorganisms that, when administered in adequate amounts, confer some benefit to the host.[1,2] Some probiotics reduce the duration and frequency of respiratory tract infections, while others indicate that they offer no benefits.[3,4] Probiotics are thought to adhere to the intestinal mucosal lining, thus preventing infectious microorganisms from adhering and causing disease. However, the mechanism at the respiratory tract level is unclear and there are even studies that report no significant changes in cytokines after the use of probiotics for RTIs.[4] Respiratory tract diseases are common in Ecuador and other developing countries. Malnutrition, low vaccination coverage, poor access to

specialized healthcare, poverty and other factors play a fundamental role in the emergence of these diseases. They are a public health problem, generating a high cost to the healthcare system due to the large number of patients that increase year after year, directly affecting the morbidity and mortality of each country.[5]

Probiotics have been used to control the growth of potentially pathogenic bacteria, increase the number of beneficial bacteria and restore lost metabolic activity.[6] In 2011, a systematic review and meta-analysis of 10 randomized controlled trials involving 3,451 participants was published, evaluating the use of probiotics to prevent respiratory tract infections in children and adults. The study found that probiotics were superior to placebo, reducing the number of RTI episodes and unnecessary antibiotic use. However, the meta-analysis did not evaluate the effect of different probiotic strains. Respiratory tract infections can be caused by viruses, bacteria and fungi. There is a symbiosis of highly pathogenic microorganisms with the normal microbiota that benefits the host. Multiple studies have shown that intestinal dysbiosis produces an alteration in the immune system and increases the risk of developing respiratory tract infections.[7,8]

Probiotic intake can modify the intestinal microbiota and consequently generate a positive activation of the immune system. Their effectiveness has been shown to be beneficial in infectious processes such as antibiotic-induced diarrhoea, in the treatment of acute diarrhoea in children and necrotizing enterocolitis in premature new-borns. Their name is derived from their genus, species and strain. Among the most studied are Lactobacillus, Bifidobacterium and *Saccharomyces boulardii*.

REVIEW

This is a descriptive-exploratory literature review. The bibliographic search period ranged from 2014 to 2024 in electronic databases such as PUBMED, ELSEVIER and Web of Science, both in English and Spanish. The keywords used in the MesH search were: probiotics; respiratory tract diseases; microbiota.

Inclusion criteria: search terms, level of evidence, abstracts and keywords, exclusion criteria: unrelated to the topic, outside the year limit, unavailable, classifications were made by year, type of study and level of evidence. Eligibility criteria included critical reading, level of evidence, documents available for analysis and relevance to the topic. A total of 32 sources were obtained for analysis and synthesis.

The main respiratory tract infections include rhinitis, tonsillitis, sinusitis, otitis media and pharyngitis. Their most frequent complications were fever, cough, sneezing, rhinorrhea, headache, pneumonia and bronchitis. Studies conducted in pediatric patients show that when probiotics are administered in combination, there is a significant reduction in the incidence of respiratory tract infections or their complications. Following the administration of probiotics, a decrease in the rates of respiratory tract infections was observed, especially in rhinitis, sinusitis and lung parenchymal infections.[9]

A randomized controlled trial conducted by Araujo et al, showed that infants who were administered probiotics for 5 or 6 months had a lower rate of recurrence of RTI episodes, with a reduction in symptoms and duration of the illness. Skovbjerg et al, indicated the use of probiotics for 10 days with a decrease in the rate of respiratory tract infections, while Rautava et al, administered them for 10 to 12 months and reported a marked reduction in the incidence of otitis media cases in infants. Similarly, et al, used probiotics for two months in their study and found a lower number of RTI cases. Table 1 compares the reduction in RTIs before and after the use of probiotics.[10-12]

Mechanism of action of probiotics in respiratory tract infections

The vast majority of studies have been conducted in mice. Probiotics help maintain the integrity of the intestinal mucosa, thus hindering the absorption of viruses and bacteria. These benefits are due to their cellular and humoral immunomodulatory role through the production of cytokines and pro-inflammatory cytokines. After oral administration of *Lactobacillus casei* to mice infected with influenza, a significant decrease in viral load was observed.

There was an increase in interferon (IFN) and tumor necrosis factors.[13] Probiotics can also act by inducing the synthesis of immunoglobulins in blood and respiratory secretions. In animals infected with Pseudomona aeruginosa pneumonia, the production of regulatory T cells increased after administration of Lactobacillus.[14]

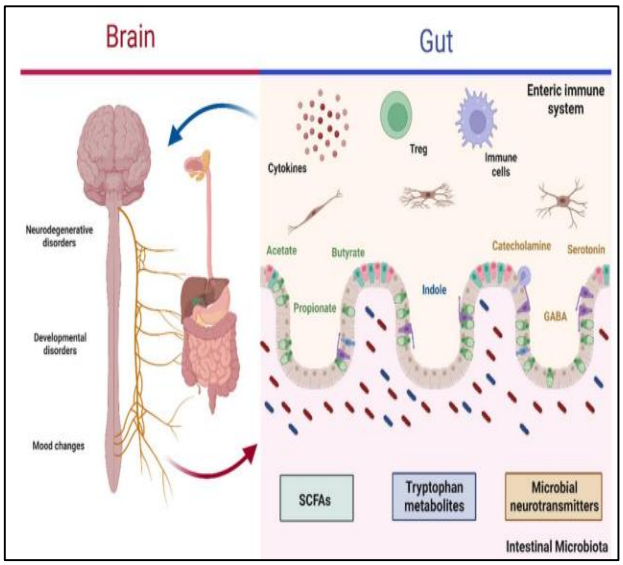

Figure 1: Mechanism of action of probiotics in respiratory tract infections.

Probiotics used in pediatric patients

In India, a randomized, double-blind, placebo-controlled study was conducted in 4,500 newborns who were administered Lactobacillus plantarum for a period of one week. A significant reduction in the sepsis-to-death ratio was observed, the primary endpoint of this study.[15] In 2022, Cochrane published a systematic review that included 6,950 people ranging in age from children (1 to 11 years), adults with a mean age of 37 years and elderly people with a mean age ranging from 84 years.

Two strains were used: *Lactobacillus plantarum* and *Lactobacillus paracasei*, administered for over three months. The authors conclude that, compared to placebo, probiotics can reduce the number of respiratory infections and the duration of RTIs.[16]

Probiotics in the gut-brain axis

The stomach and the brain interact in various ways, achieving optimal communication through the vagus nerve, which leaves the stomach with information that is processed in the nucleus of the solitary tract, enabling a feedback mechanism based on the information obtained from the stomach. Studies conducted in mice support this fact with evidence. They use water avoidance stress models and, by using *Lactobacillus casei*, provoke the activity of the gastric branch of the vagal afferent to activate corticotropin-releasing factor.[16]

Peripheral regulatory T cells, as well as their maintenance, induction and intestinal immune homeostasis, are regulated by signals captured by the vagal reflex, belonging to the hepatic vagal sensory afferents, which detect the intestinal microenvironment. The various uses of probiotics have demonstrated their appropriate interaction between different systems and organisms. They serve as enzymatic, immune and stress modulators, impacting systems such as the gastrointestinal, respiratory and neurological systems.[16] The gut microbiota, as well as its metabolites, influences brain, hematologic, humoral and immune functions through neuronal pathways. Likewise, there is variation in the composition of microorganisms and their taxonomy among different organisms, depending on their needs to maintain proper homeostasis. Figure 1 shows the interaction between the gut microbiota and the various disorders in which the vagus nerve is involved, such as neurological disorders, developmental disorders, mood swings and others.

Probiotics for lower respiratory conditions

In recent years, respiratory diseases have taken on significant importance due to complications and the death of millions of people, becoming the sixth leading cause of mortality in all age groups. There are more than 200 types of viruses, both DNA and RNA. There are viruses that affect the upper respiratory tract (RSV) and lower respiratory viruses (LRV). However, systematic reviews have concluded that RSV viruses contribute to bacterial colonization in LRVs, but the infection rate has not been quantified.[17,18] Among the viruses, COVID-19 stands out, which triggered a pandemic in 2020. It is an RNA virus known as SARS-CoV-2. It is a type of enveloped, single-stranded coronavirus that has four genera (α, β, γ and δ). When a person contracts the disease, they generate an immune response known as a cytokine storm due to diffuse bilateral alveolar destruction, hyaline membrane formation, pneumocyte desquamation and fibrin deposits in both lungs. Bacteria such as Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis also cause pneumonia, primarily in infants and children. Pneumonia is characterized by chronic inflammation in the pulmonary pleura and in the final stages of the disease, fluid accumulation limits lung function.[17]

The immune system responses that play an important role in viral elimination include type I interferon and CD4 and CD8 T lymphocytes. There is also evidence that probiotic microorganisms can modulate components of the immune system, as they are live microorganisms, influencing the composition of the intestinal microflora and positively regulating the pulmonary microbiota. such as *Lactobacillus rhamnosus* GG (LGG) and Lactobacillus casei strains Shirota (LcS) and DN114001, modulates immune homeostasis, mitigating the effects of bacterial and viral infections; Likewise, Bifidobacterium or Lactobacillus at the level of VRI minimizes the activation of pro-inflammatory and anti-inflammatory cytokines, favoring viral elimination and aiding a speedy recovery.[19] A studied complication is when viruses enter epithelial cells, where they replicate and interrupt cellular processes that end in cell lysis, generating damage to the epithelial layer and the basement membrane. This induces an increase in the inflammatory response and in the expression of adhesion proteins in epithelial cells. After that moment, bacteria such as *S. pneumoniae* and *H. influenzae* can enter the host because they express their own phosphorylcholine receptor ligand and platelet-activating factor, worsening the patient's clinical picture.[20]

Table 1: Comparison of the reduction in respiratory tract infections before and after the use of probiotics.

Diagnosis	Before using probiotics frequency %	After using probiotics frequency %	% decreased in RTIs
Rhinitis	21-30	9-12	17
Otitis	17-24	7-10	10
Tonsillitis	15-21	6-8	12
Bronchitis	11-15	4-5	10
Pneumonia	6-8	3-4.29	4.28

DISCUSSION

Safety of probiotics

The vast majority of probiotics currently in use come from fermented foods or microbes that colonize healthy humans. They have been used for decades in various products. Based on the high prevalence of lactobacilli in fermented foods, these are natural and normal colonizers of the human body and they are also attributed with a low level of infection. Due to all these benefits, experts have considered their pathogenic potential to be low, which is why their application in the field of medicine has been widely studied.[21]

As an example, we have Bifidobacterium. These bacteria have a proven safety record, with most of these products intended for the general healthy population. Their use in people with immunosuppression or who suffer from serious underlying diseases requires restrictions.[25] Formulations with traditional probiotics have long been associated with food fermentation, which is why they are considered safe for oral consumption in formulations with foods and supplements for the generally healthy population and at the levels traditionally used.[22]

Several European agencies responsible for safety regulation, such as the EFSA (European Food Safety Authority) for nutritional supplements or the EMA (European Medicines Agency) for medicines, are required. meet EFSA's QPS (Qualified Presumption of Safety) standards. In the US, these products must meet the FDA's GRAS (Generally Recognized as Safe) standards.[23] For safety and quality assessment, studies are based on reasonable evidence. This is also required for probiotic products with a long history of use, as well as for older products. The QPS list is reviewed annually, allowing for the inclusion of new probiotic species.[24]

Probiotics in infant formula

Probiotics are live microorganisms whose adequate amounts can benefit the host's health. A probiotic commonly known as *Lactobacillus rhamnosus* GG (LGG) is also known as *Bifidobacterium lactis*. The potential benefits of administering probiotics to children have been recognized worldwide. Some probiotic strains have been shown to be beneficial in the treatment or prevention of certain pediatric diseases.[26]

Studies suggest that, depending on the type of delivery, the intestinal microbiota varies. In the case of vaginal delivery, babies have a gut microbiota similar to the mother's vaginal microbiota, in the case of cesarean delivery, the microbiota is similar to the mother's skin microbiota. Babies born by cesarean section tend to have higher amounts of microorganisms such as Clostridium and other potentially pathogenic bacteria and lower amounts of Bifidobacteria and Bacteroides. These variations gradually disappear between 6 and 14 months.[27] It is known that, due to various factors, some infants and new-borns cannot benefit from breastfeeding. Therefore, the goal of these dairy industries is to ensure the production of infant formulas that are similar to breast milk in both composition and physiological properties. Breast milk has certain bioactive compounds that are unique and specific to human milk and these bioactive compounds, such as cytokines and growth factors, are associated with childhood health outcomes such as food allergies.[28] Due to cost and stability, these compounds cannot be added to formulas. However, supplementation with prebiotics or live bacteria that promote health is more conventional and easier to improve infant formula. Because breastfed infants already have a microbiota containing Bifidobacterium, the first strategy is to add specific probiotics, such as Bifidobacterium, directly to infant formula.

This should follow a cycle, meaning that prebiotics, symbiotic and postbiotics are then added due to their bifidogenic effects, which will contribute positively to the infant's immunity. Currently in France, more than 50% of infants are fed probiotic-enriched infant formulas.[29]

Intestinal colonization during infant birth promotes long-term health by modulating the immune system. The immune system is strengthened by probiotics because they can simulate and mimic the effects of breast milk, promoting a similar microbiota and strengthening infant immunity. The oligosaccharides in human milk help stimulate the production of bifidobacteria and, in turn, their growth.

They also contribute to the production of short-chain fatty acids (SCFAs). This process supports intestinal function and infant immunity. It is important to mention that the intestinal microbiota stimulates the development of gut-associated lymphoid tissue, making this development crucial for infant immunity. Infant formula (IF) is considered a substitute for human breast milk and is formulated to mimic its composition

Human breast milk is composed of 87% water, 3.8% fat, 1% protein and 7% lactose, unlike infant formula, which is generally cow's milk and contains more protein and fewer carbohydrates than human breast milk.[6,7] It is essential to emphasize that carbohydrates are essential energy sources for infant growth. These compositional differences are important to consider because they can cause growth difficulties in infants and cause various diseases.

This novel approach to supplementing infant formula with prebiotics, probiotics and micronutrients aims to close this compositional gap. Certain studies have shown evidence that certain additives used in infant formula can improve intestinal health and infant growth, although the results are mixed and certain effects have not yet been confirmed. The function of prebiotics (galactooligosaccharides and fructooligosaccharides) favors the increase in bifidobacteria in the infant's gut, while probiotics

(*Bifidobacterium animalis*, *Lactobacillus rhamnosus* GG) can modify the gut microbiota to resemble that of infants fed with breast milk.[31]

The gut microbiota is a set of live microorganisms that help regulate metabolism, contribute to nutrient absorption and support the immune system[11] Breast milk contributes a microbiome dominated by bifidobacteria, whereas infant formula may have a more diverse but unstable gut microbiota. Therefore, probiotic supplementation is functional and beneficial for the gut microbiota.[32]

CONCLUSION

Multiple probiotics are used consistently to prevent or reduce the number of cases or severity of various respiratory tract infections. Only Lactobacillus casei has shown efficacy against infections, necessitating further studies to help support its use in daily practice. All studies conducted in animals or humans indicate some beneficial effect on the use of probiotics, none report adverse effects, making their use safe. The time to implementation is unclear; on the contrary, real benefits are found after six months of implementation.

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