Narrative review articles

Immune modulation in allergic diseases associated with the use of *Bifidobacterium* in children under 5 years of age

DOI: 10.5377/alerta.v5i1.12563

José Antonio Mitjavila Samayoa[1]*, Liliana Esmeralda Henríquez Benítez[2], María Gabriela Valencia Joya[3], Zayri Geraldine García Meléndez[4]

1-4. Universidad Dr. José Matías Delgado, Antiguo Cuscatlán, La libertad, El Salvador

*Correspondence
jose_mitjavila@hotmail.com

1. 0000-0001-8856-7957
2. 0000-0002-2041-7212
3. 0000-0002-8253-7949
4. 0000-0002-9609-9433

Abstract
The incidence of allergic diseases in childhood is increasing and has become one of the main reasons for consultations. One possible cause is dysbiosis of the gut microbiome, related to increased inflammatory states. Due to the need to improve quality of life, and the impact on economic and educational aspects, probiotics have emerged as an adjuvant treatment, hence the aim is to identify the association between the use of *Bifidobacterium* in children under 5 years old age with the modulation of the immune response in allergic diseases. The intestinal microbiome begins its development and maturation from gestation, continues at birth and ends at 3 years of age, influenced by maternal, neonatal and environmental factors. The intestinal dysbiosis generated by these factors reduces the proportion of bifidobacteria, which is related to pro-inflammatory states. Consequently, studies on the use of *Bifidobacterium* in children with allergic diseases have shown improvement of symptoms and quality of life. Probiotics favor a healthy intestinal microbiome, associated with an anti-inflammatory state, due to the regulation of the Th1 / Th2 / T regulatory, cell balance and natural killer cells. This modulation in the immune response allows better symptoms control, quality of life and a lower incidence of allergic diseases in childhood.

Keywords
Gastrointestinal microbiome, *Bifidobacterium*, probiotics.

Resumen
La incidencia de enfermedades alérgicas en la infancia va en aumento y se ha convertido en una de las principales consultas. Una posible razón es la disbiosis del microbioma intestinal, relacionada con estados inflamatorios incrementados. Debido a la necesidad de mejorar la calidad de vida, impacto en lo económico y educativo, surgen los probióticos como tratamiento adyuvante, por lo que se pretende identificar la asociación del uso de *Bifidobacterium* en menores de 5 años con la modulación de la respuesta inmune en enfermedades alérgicas. El microbioma intestinal inicia su desarrollo y maduración desde la gestación, continúa en el nacimiento y termina hasta los 3 años, influenciado por factores maternos, neonatales y ambientales. La disbiosis intestinal generada por estos factores reduce la proporción de bifidobacterias, lo cual se relaciona con estados proinflamatorios. En consecuencia, estudios acerca del uso de *Bifidobacterium* en niños con enfermedades alérgicas ha evidenciado mejoría de síntomas y calidad de vida. Los probióticos favorecen un microbioma intestinal saludable, asociado a un estado antiinflamatorio, debido a la regulación en el balance celular Th1/Th2/T reguladoras y células asesinas naturales. Esta modulación en la respuesta inmune permite un mejor control de síntomas, calidad de vida y menor incidencia de enfermedades alérgicas en la infancia.

Palabras clave
Microbioma gastrointestinal, *Bifidobacterium*, probióticos.

Introduction

Dysbiosis of the intestinal microbiome is related to alteration of the adaptive immune response[1], whose changes generate modifications in immune tolerance[2], polarized imbalance towards Th2, immune hyperreactivity[3] and, consequently, an increased inflammatory response that culminates in the development of allergic diseases[4]. The prevalence in pediatric age has increased in recent years.

OPEN ACCESS

Modulación inmune en enfermedades alérgicas asociada al uso de *Bifidobacterium* en menores de cinco años

Suggested citation:
Mitjavila Samayoa JA, Henríquez Benítez LE, Valencia Joya MG, García Meléndez ZG. Immune modulation in allergic diseases associated with the use of *Bifidobacterium* in children under 5 years of age. Alerta. 2022;5(1):43-49. DOI: 10.5377/alerta.v5i1.12563

Received:
September 16, 2021.

Accepted:
October 11, 2021.

Published:
January 27, 2022.

Author contribution:
JAMS[1]: study conception, manuscript design and data analysis. LEHB[2]: bibliographic search and data collection. MGVJ[3]: data handling or software. ZGGM[4]: drafting, revising and editing

Conflicts of interest:
There are no financial relationships with entities or institutions in health that represent a conflict of interest.

According to the World Health Organization (WHO), asthma is the most frequent chronic disease in this population[5], with an annual mortality of approximately 250,000 deaths that were mostly preventable[6]. Eczema has tripled in prevalence, affecting 1 in 5 children[7], and allergic rhinitis has become one of the main causes of consultation in pediatric patients due to the difficult control of symptoms[8]. It is necessary to improve the quality of life, reduce the economic and educational impact around allergic diseases in middle- and low-income countries[9].

Probiotics are microorganisms that, when properly administered, can create benefits[10], such as modifying the immune response[11] and preventing or improving intestinal dysbiosis, thus reducing the risk of acute or chronic allergic diseases[12]. The most studied probiotics are: *Bacillus* spp., *Lactobacillus* spp., *Bifidobacterium* spp., *treptococcus* spp., and *Propionibacterium* spp., and *Propionibacterium* spp. They can be found in food products and influence nutritional metabolism and the physiological function of the host[13].

Probiotics have been used as adjuvants in the management of allergic diseases[14]. For this reason, it is intended to identify the association of the use of *Bifidobacterium* in children under 5 years with the modulation of the immune response in allergic diseases.

Discussion

Characteristics of the gut microbiome in children under the age of five

The gut microbiome is composed of bacteria, viruses, fungi and protozoa, which contribute to the biosynthesis of amino acids, vitamins and metabolites, which are part of its structural elements[15]. Its development begins in gestation and lasts during the first 3 years of life, until it reaches a mature microbiome, like the adult[16]; however, during this process there may be changes influenced by different genetic factors, such as gestational diabetes, use of antibiotics, delivery route, prematurity[17] and type of feeding in the first years of life, generating intestinal dysbiosis[18].

The delivery route is one of the main factors associated with the composition of the neonatal microbiome[19]. Vaginal birth allows contact with the maternal fecal and vaginal flora, dominated by species such as *Lactobacillus*, *Bifidobacterium* and *Bacteroides*, which improve immune function and reduce the inflammatory response[20]. There is contact with maternal skin and environmental microorganisms[21], such as *Enterococcus*, *Staphylococcus epidermidis*, *Streptococcus paradanguinis*, *Klebsiella* spp., *Enterobacter cloacae* and *Clostridium perfringens* by caesarean section [22].

In 2016, Domínguez *et al.* found that controlled exposure to vaginal secretions in neonates born by cesarean section generates a change in the composition of the microbiome during the first months, enriching itself with *Lactobacillus* and *Bacteroides*[23]. Similarly, in 2015 Backhed *et al.* detailed the composition of the gut microbiome during the first year of life. Evaluating samples from 98 mothers and their healthy children born vaginally or by cesarean section showed that from the fourth month of life the difference in the microbiome between both birth routes was more heterogeneous, until progressing to a mature microbiome similar to the adult, influenced by a diet based on breastfeeding[24].

As for food, if it is inadequate in the first 6 months of life, it can cause malnutrition in children under 2 years of age, therefore, a deficiency in the development of the intestinal microbiome can be caused[25]. Therefore, breastfeeding-based nutrition is important, since it provides immunoglobulins that help in the maturation of the immune system and oligosaccharides that degrade short-chain fatty acids, which are directly related to the number of *Bifidobacterium*, allowing greater fermentation of oligosaccharides in the colon[26].

The introduction of complementary feeding initiates gradual changes in the composition, diversity and maturation of the intestinal microbiome, increasing the percentage of *Bacteroides* spp and *Clostridium*[27] and decreasing the *Bifidobacterium* family. However, the later one remains metabolically important in the adult microbiome.

The use of antibiotics at an early age decreases the amount of bifidobacteria and increases the percentage of gram-negative *Enterococcusy*, which increases the predisposition to metabolic, inflammatory and immunological diseases[28].

The development of the intestinal microbiome in prematurity is divided into 4 phases: the first by *Staphylococcus*, followed by *Enterococcus, Enterobactericeae*, until reaching the last phase of *Bifidobacterium*[29]. Therefore, preterm infants are a group with alteration of the intestinal microbiome that, in addition to having a higher percentage of pathogenic bacteria, are exposed for a longer time to a hospital environment, antibiotics and different types of diet[30]. Also, they have a marked increase in proteobacteria compared to *Bifidobacterium* and *Bacteroides*[31], which causes alterations in intestinal

permeability, immune response to vaccines and growth, favoring pro-inflammatory states[32]. Therefore, in premature infants, probiotics, when administered through breastfeeding or supplemented formulas, can avoid complications or reduce the risk of necrotizing enterocolitis.

Exclusive breastfeeding and maternal education on nutrition, hygiene and early stimulation33 allow the development of the mature intestinal microbiome with a predominance of bifidobacteria, which generates positive changes in cognitive development and child growth[34], especially in populations with malnutrition in developing countries or low resources. Similarly, the presence of older siblings or pets can contribute to the development of the infant gut microbiome[35]. Exposure to these generates an excess of *Clostridium* spp, *Veillonella*, *Peptostreptococcaceacey Coprococcusy* subspecies of *Bifidobacterium* in the intestine of the infant[36].

Effect of *Bifidobacterium* on the immune system response

Over the past few years the use of probiotics has been on the rise. Its safety and effects on the immune system have been deeply investigated. In 2017, Manzano *et al.* contrasted different strains of probiotics, including two types of *Bifidobacterium* (*Bifidobacterium longum* subsp. *infantis* and *Bifidobacterium bifidum*). Also, *Lactobacillus helveticus*, against a placebo control group. Their report indicates that the consumption of these in childhood is safe, well tolerated (p <0,001) and the growth is not altered (p <0,05)[37].

In 2016, Wu *et al.* studied 264 healthy neonates with 0 to 7 days of age fed with formula and it was determined the effect of *Bifidobacterium longum* supplementation on gut microbiome composition and immune system development. It was showed the supplementation group significantly increased the number of bifidobacteria and the bifidobacteria/enterobacteria ratio through the analysis of blood and stool samples in the first four months, unlike the control group. Also, it was reported an increase in the secretion of interferon-γ (p =0,004), the main cytokine produced by Th1 lymphocytes, and it was discussed that the proper use of bifidobacteria in early stages could generate a healthy microbiome in non-lactating neonates, as well as an adequate balance between the Th1/Th2 immune response, thus reducing the risk of allergic diseases[38].

On the one hand, De Andrés *et al.* conducted a study with 202 infants aged 3-12 months to demonstrate the modulating effect of probiotics on the immune system by comparing supplementation with 3 different strains of *Bididobacterium* and *Lactobacillus* against a placebo; when analyzing the concentrations of cytokines, chemokines, growth factors and immunoglobulins in stool samples, they showed that the predominance of *Bifidobacterium* in the intestinal microbiome, favored by the administration of probiotics, increases the ratio of IL-10/IL-12, and relates its decrease to a pro-inflammatory state (p <0,001)[39]. But on the another hand, the placebo group due to the lack of supplementation presented an increase in TNF-α/IL-10 and generated an immune response contrary to that of the control group (p <0,001).

Similar results were described in older populations in the study by Lee *et al.*, in 2017, where they compared the daily administration of the probiotics *Lactobacillus paracasei* spp. *paracasei* (*L. paracasei*), *Bifidobacterium animalis* spp. lactis (*B. lactis*) and *Lactobacillus plantarum* (*L. plantarum*), integrated into yogurt for 12 weeks against a control group. They found that the absence of probiotic supplementation favors a pro-inflammatory state due to increased activity of natural killer (NK) cells (p <0,001) and increased serum level of IL-12, IFN-γ (p =0,041) and IgG1 (p =0,022) in the control group[40].

Similarly, Chowdhury *et al.* reported that the simultaneous administration of probiotics (*Bifidobacterium longum* and *Lentinula edodes micelios*) generates a polarization towards an anti-inflammatory state when compared to a placebo, noting an increase in the activity of regulatory T cells (p =0,046)[41].

As well as modulating the overall immune response, probiotics can directly generate changes in the local immune response. In 2019, Xiao *et al.* conducted a study in infants aged 3,5-6 months in good health, whose diet was 80 % formula-based. At the beginning, they showed decreased levels of intestinal immunoglobulin A (IgA). When including probiotic supplementation (*Bifidobacterium infantis*, *Bifidobacterium bifidum* and *Lactobacillus helveticus*), the IgA concentration remained at high levels compared to the control group (p <0,0044)[42].

Effects of *Bifidobacterium* supplementation on the control of allergic diseases

The use of probiotics such as *Bifidobacterium* sp. has gained importance in public health as an adjuvant treatment in the primary prevention of allergic diseases in pe-

diatric patients[43], with interventions even before birth.

In 2019, Kim *et al.* compared the effect of *Bifidobacterium longum*, *Lactobacillus plantarum*, a mixture of both probiotics, a placebo control in mice with induced allergic rhinitis and demonstrated the three groups used probiotics presented a significant improvement in symptoms, lower levels of IL-4 and IL-5 intranasal and bronchoalveolar, as well as a decrease in blood IgE and eosinophils, mast cells and Th2[44].

In 2010, Dotterud *et al.* presented a placebo-controlled clinical trial conducted in 415 pregnant women and found that infants who consumed breastfeeding from mothers treated with probiotics had a lower probability ratio of developing atopic dermatitis (OR =0,51) and significant decrease in severity (p <0,05) compared to the control group [45].

In 2014, Similar results were obtained in the open-label study by Enotomo *et al.*, conducted with 166 healthy pregnant women, in which they compared the supplementation of a mixture of bifidobacteria against a control group. Bifidobacteria were administered to mothers 4 weeks before the due date and to neonates from 1 week after birth to 6 months of age. It was discovered that the treated group had a lower prevalence of eczema at less than 10 months (p =0,007) and 18 months (p =0,033)[46].

Primary prevention interventions have also shown benefits when applied in late childhood. In 2019, Schmidt *et al.* conducted a clinical trial in 290 healthy children with an average age of 10 months, comparing the 6-month use of a combination of lactobacilli and bifidobacteria against a placebo control. They reported that the treated group had a lower incidence of eczema (p =0,036) compared to the control group[47].

Del Giudice *et al.* conducted a clinical trial in 40 children with pollen-induced allergic rhinitis and intermittent allergy asthma, comparing a mixture of bifidobacteria against a placebo control during four weeks. They assessed as outcomes the relief of nasal symptomatology and the improvement in quality of life. The treated group presented significant improvement in symptoms (p <0,005) and quality of life (p <0,001), while the control group presented worsening in both parameters[48].

Research in older populations shows similar effects with the use of probiotics. In 2021, Anania *et al.* conducted a prospective study in 250 patients aged 6-17 years with a diagnosis of allergic rhinitis, comparing the use for 3 consecutive months of a mixture of bifidobacteria and enterococci against a placebo control. It was evidenced that the treated group presented a significant improvement in nasal symptoms (p =2,2x10-10), a reduction in the use of oral antihistamines (p =<0,001) and topical corticosteroids (p =<0,001)[49].

In 2020 Kang *et al.* conducted a clinical trial in 95 adults with allergic rhinitis in which they compared a mixture of bifidobacteria and lactobacilli against a placebo control. They administered them as monotherapy for 4 weeks and significant improvements in nasal symptoms (p =0,029), in the marker of immune response (p =0,047) and in the proportions IL-10/IL-4 and IL-10/IL-13, p =0,046 and p =0,018, were presented at the end of the management [50].

Conclusión

The use of probiotics favors a healthy intestinal microbiome, associated with an anti-inflammatory state in the body, due to the regulation in the immune system by different routes, mainly through the cellular balance Th1/Th2/T regulators and NK. This modulation in the immune response decreases the incidence of common allergic diseases in childhood, such as allergic rhinitis, asthma and eczema.

Funding

There are no funding sources, agreements or possible conflicts of interest.

References

1. Fujimura KE, Sitarik AR, Havstad S, Lin DL, Levan S, Fadrosh D, *et al*. Microbioma intestinal neonatal asociado con la atopia multisensibilizada infantil y la diferenciación de células T. Nat Med. 2016;22(10):1187-91. DOI: 10.1038/nm.4176
2. Lee-Sarwar KA, Kelly RS, Lasky-Su J, Zeiger RS, O'Connor GT, Sandel MT, *et al*. Análisis integrativo del metoboloma intestinal del asma infantil. J Allergy Clin Immunol. 2019;144(2):442-54. DOI: 10.1016/j.jaci.2019.02.032
3. Vidova V, Benesova E, Klanova J, Thon V, Spacil Z. Perfiles cuantitativos simultáneos de marcadores inmunes clínicamente relevantes en hisopos de heces neonatales para revelar inflamación. Sci Rep. 2021;11(1):1-9. DOI: 10.1038/s41598-021-89384-0
4. Russell SL, Gold MJ, Willing BP, Thorson L, McNagny KM, Finlay BB. El tratamiento con antibióticos perinatales afecta la microbiota murina, la respuesta inmunitaria y el asma

alérgico. Gut Microbes. 2013;4(2):158-64. DOI: 10.4161/gmic.23567
5. Herrera AM, Cavada Ch G, Mañalich M J. Hospitalizaciones por asma infantil en Chile: 2001-2014. Rev Chil Pediatría. 2017;88(5):6027- DOI: 10.4067/s0370-41062017000500005
6. Pawankar R, Canonica GW., Holgate ST., Lockey RF. Libro Blanco sobre Alergia de la WAO. 2011:26. Disponible en: https://www.worldallergy.org/UserFiles/file/WWBOA_Executive-Summary_Spanish.pdf
7. Chalmers JR., Haines RH., Bradshaw LE., Montgomery AA., Thomas KS., Brown SJ., *et al*. Emolientes diarios durante la infancia para la prevención de eccema: ensayo controlado aleatorizado BEEP. Lancet Lond Engl. 2020;395(10228):962-72. DOI: 10.1016/S0140-6736(19)32984-8
8. Álvarez Paneque O., Parra Cruz M., Martínez Ramírez R., Ochoa Roca TZ., Chapman Taberas M. Evaluación clínica de niños con rinitis alérgica tratados con montelukast. Correo Científico Méd.2016;20(3):452–67. Disponible en: http://scielo.sld.cu/scielo.php?script=sci_abstract&pid=S1560-43812016000300002&lng=es&nrm=iso&tlng=en
9. Yang-Huang J., Van Grieken A., Van Meel ER., He H., De Jongste JC., Duijts L., *et al*. Factores sociodemográficos, asma actual y función pulmonar en una población infantil urbana. Eur J Clin Invest.2020;50(10). DOI: 10.1111/eci.13277
10. Cabana MD., McKean M., Caughey AB., Fong L., Lynch S., Wong A., *et al*. Suplementación temprana con probióticos para la prevención del eccema y el asma: un ensayo controlado aleatorio. Pediatrics. 2017;140(3). DOI: 10.1542/peds.2016-3000
11. Kepert I., Fonseca J., Müller C., Milger K., Hochwind K., Kostric M., *et al*. El D-triptófano de bacterias probióticas influye en el microbioma intestinal y en la enfermedad alérgica de las vías respiratorias. J Allergy Clin Immunol. 2017;139(5):1525-35. DOI: 10.1016/j.jaci.2016.09.003
12. Durack J., Kimes NE., Lin DL., Rauch M., McKean M., McCauley K., *et al*. El retraso en el desarrollo de la microbiota intestinal en lactantes de alto riesgo de asma se puede modificar temporalmente mediante la suplementación con *Lactobacillus*. Nat Commun. 2018;9(1):707. DOI: 10.1038/s41467-018-03157-4
13. Kim MJ., Ku S., Kim SY., Lee HH., Jin H., Kang S., *et al*. Evaluación de seguridad de *Bifidobacterium bifidum* BGN4 y *Bifidobacterium longum* BORI. Int J Mol Sci. 2018;19(5):1422. DOI: 10.3390/ijms19051422
14. Barthow C., Wickens K., Stanley T., Mitchell EA., Maude R., Abels P., *et al*. Estudio de Probióticos en el Embarazo (PiP Study): justificación y diseño de un ensayo controlado aleatorio doble ciego para mejorar la salud materna durante el embarazo y prevenir eccema y alergia infantil. BMC Pregnancy Childbirth. 2016;16. DOI: 10.1186/s12884-016-0923-y
15. Singh RK., Chang H-W., Yan D., Lee KM., Ucmak D., Wong K., *et al*. Influencia de la dieta en el microbioma intestinal y las implicaciones para la salud humana. J Transl Med. 2017;15(1):73. DOI: 10.1186/s12967-017-1175-y
16. Milani C., Duranti S., Bottacini F., Casey E., Turroni F., Mahony J., *et al*. Primeros colonizadores microbianos del intestino humano: composición, actividades e implicaciones para la salud de la microbiota intestinal infantil. Microbiol Mol Biol Rev MMBR. 2017;81(4). DOI: 10.1128/MMBR.00036-17
17. Barrett E., Kerr C., Murphy K., O'Sullivan O., Ryan CA., Dempsey EM., *et al*. La naturaleza individual y diversidad de la microbiota del lactante prematuro. Arch Dis Child - Fetal Neonatal Ed. 2013;98(4):F334–40. DOI: 10.1136/archdischild-2012-303035
18. Wang J., Zheng J., Shi W., Du N., Xu X., Zhang Y., *et al*. Disbiosis del microbioma materno y neonatal asociado con diabetes *mellitus* gestacional. Gut. 2018;67(9):1614–25. DOI: 10.1136/gutjnl-2018-315988
19. Lim ES., Wang D., Holtz LR. Los Hitos del microbioma bacteriano y del viroma en el desarrollo infantil. Trends Microbiol. 2016;24(10):801–10. DOI: 10.1016/j.tim.2016.06.001
20. Butler ÉM., Chiavaroli V., Derraik JGB., Grigg CP., Wilson BC, Walker N, *et al*. Bacterias maternas para corregir la microbiota intestinal anormal en bebés nacidos por cesárea. Medicine (Baltimore). 2020;99(30). DOI: 10.1097/MD.0000000000021315
21. Sordillo JE., Zhou Y., McGeachie MJ., Ziniti J., Lange N., Laranjo N., *et al*. Factores que influyen en el microbioma intestinal del lactante entre los 3 y 6 meses de edad: resultados del ensayo de reducción del asma prenatal con vitamina D (VDAART) étnicamente diverso. J Allergy Clin Immunol. 2017;139(2):482-491.e14. DOI: 10.1016/j.jaci.2016.08.045
22. Shao Y., Forster SC., Tsaliki E., Vervier K., Strang A., Simpson N., *et al*. Cambios en la microbiota y colonización de patógenos oportunistas en el parto por cesárea. Nature. 2019;574(7776):117-21. DOI: 10.1038/s41586-019-1560-1
23. Domínguez-Bello MG., De Jesús-Laboy KM., Shen N., Cox LM., Amir A., González A., *et al*. Restauración parcial de la microbiota de los recién nacidos por cesárea mediante transferencia microbiana

vaginal. Nat Med. 2016;22(3):250-3. DOI: 10.1038/nm.4039
24. Bäckhed F., Roswall J., Peng Y., Feng Q., Jia H., Kovatcheva-Datchary P., *et al*. Dinámica y estabilización del microbioma intestinal humano durante el primer año de vida. Cell Host Microbe. 2015;17(5):690–703. DOI: 10.1016/j.chom.2015.04.004
25. Gehrig JL., Venkatesh S., Chang H-W., Hibberd MC., Kung VL., Cheng J., *et al*. Efectos de los alimentos dirigidos a la microbiota en animales gnotobióticos y niños desnutridos. Science. 2019;365(6449). DOI: 10.1126 /science.aau4732
26. Illiano P., Brambilla R., Parolini C. La interacción mutua de la microbiota intestinal, la dieta y las enfermedades humanas. FEBS J. 2020;287(5):833–55. DOI: 10.1111/febs.15217
27. Wopereis H., Oozeer R., Knipping K., Belzer C., Knol J. Los primeros mil días-microbiología intestinal de la vida temprana: estableciendo una simbiosis. Pediatr Allergy Immunol. 2014;25(5):428-38. DOI: 10.1111/pai.12232
28. Korpela K., Salonen A., Vepsäläinen O., Suomalainen M., Kolmeder C., Varjosalo M., *et al*. La suplementación con probióticos restaura la composición y función normales de la microbiota en los bebés tratados con antibióticos y en los nacidos por cesárea. Microbiome. 2018;6. DOI: 10.1186/s40168-018-0567-4
29. Korpela K., Blakstad EW., Moltu SJ., Strømmen K., Nakstad B., Rønnestad AE., *et al*. Desarrollo de la microbiota intestinal y edad gestacional en recién nacidos prematuros. Sci Rep. 2018;8(1):2453. DOI: 10.1038/s41598-018-20827-x
30. Dermyshi E., Wang Y., Yan C., Hong W., Qiu G., Gong X., *et al*. La "edad de oro" de los probióticos: una revisión sistemática y un metaanálisis de estudios aleatorizados y observacionales en infantes prematuros. Neonatology. 2017;112(1):9–23. DOI: 10.1159/000454668
31. Pammi M., Cope J., Tarr PI., Warner BB., Morrow AL., Mai V., *et al*. Disbiosis intestinal en infantes prematuros que preceden a la enterocolitis necrotizante: una revisión sistemática y un metanálisis. Microbiome. 2017;5. DOI: 10.1186/s40168-017-0248-8
32. Underwood MA., Gaerlan S., De Leoz MLA., Dimapasoc L., Kalanetra KM., Lemay DG., *et al*. Oligosacáridos de la leche materna en lactantes prematuros: absorción, excreción e influencia en la microbiota intestinal. Pediatr Res. 2015;78(6):670–7. DOI: 10.1038/pr.2015.162
33. Atukunda P., Muhoozi GKM., Van den Broek TJ., Kort R., Diep LM., Kaaya AN., *et al*. Desarrollo, crecimiento y microbiota infantil: seguimiento de un ensayo educativo aleatorizado en Uganda. J Glob Health. 2019;9(1). DOI: 10.7189/jogh-09-010431
34. Ryan PM., Stanton C., Ross RP., Kelly AL., Dempsey E., Ryan CA. Perspectiva de pediatría en la investigación del microbioma intestinal infantil: estado actual y desafíos. Arch Dis Child. 2019;104(7):701–5. DOI: 10.1136/archdischild-2019-316891
35. Kortekangas E., Kamng'ona AW., Fan Y., Cheung YB., Ashorn U., Matchado A., *et al*. Exposiciones ambientales y microbiota intestinal materna e infantil en las zonas rurales de Malawi. Paediatr Perinat Epidemiol. 2020;34(2):161–70. DOI: 10.1111/ppe.12623
36. Martin R., Makino H., Cetinyurek Yavuz A., Ben-Amor K., Roelofs M., Ishikawa E., *et al*. Los eventos tempranos, incluido el modo de parto y el tipo de alimentación, los hermanos y el género, dan forma al microbiota intestinal en desarrollo. PLoS ONE .2016;11(6). DOI: 10.1371/journal.pone.0158498
37. Manzano S., De Andrés J., Castro I., Rodríguez JM., Jiménez E., Espinosa-Martos I. Seguridad y tolerancia de tres cepas de probióticos en infantes sanos: un ensayo multicéntrico, aleatorizado, doble ciego y controlado con placebo. Benef Microbes. 2017;8(4):569–78. DOI: 10.3920/BM2017.0009
38. Wu B-B., Yang Y., Xu X., Wang W-P. Efectos de la suplementación con *Bifidobacterium* sobre la composición de la microbiota intestinal y la respuesta inmune en infantes sanos. World J Pediatr. 2016;12(2):177–82. DOI: 10.1007/s12519-015-0025-3
39. De Andrés J., Manzano S., García C., Rodríguez JM., Espinosa-Martos I., Jiménez E. Efecto modulador de tres cepas probióticas sobre la composición microbiana intestinal y los parámetros inmunológicos de infantes en un estudio placebo control, doble ciego aleatorizado. Benef Microbes. 2018;9(4):573–84. DOI: 10.3920/BM2017.0132
40. Lee A., Lee YJ., Yoo HJ., Kim M., Chang Y., Lee DS., *et al*. El consumo de yogur lácteo que contiene *Lactobacillus paracasei ssp. paracasei, Bifidobacterium animalis ssp. lactis* y técnicamente tratado *Lactobacillus plantarum* mejora la función inmune, incluida la actividad de las células asesinas naturales. Nutrients. 2017;9(6). DOI: 10.3390/nu9060558
41. Chowdhury AH., Cámara M., Verma C., Eremin O., Kulkarni AD., Lobo DN. Modulación de fenotipos de células T reguladoras y dendríticas después de la ingestión de *Bifidobacterium longum*, AHCC y azitromicina en individuos sanos. Nutrients. 2019;11(10):2470. DOI: 10.3390/nu11102470

42. Xiao L., Gong C., Ding Y., Ding G., Xu X., Deng C, *et al*. Los probióticos mantienen los niveles de secreción intestinal de inmunoglobulina A secretora en bebés sanos alimentados con fórmula: un estudio aleatorizado, doble ciego y controlado con placebo. Benef Microbes. 2019;10(7):729–39. DOI: 10.3920/BM2019.0025
43. Tamburini S., Shen N., Wu HC., Clemente JC. El microbioma en la vida temprana: implicaciones para los resultados de salud. Nat Med. 2016;22(7):713–22. DOI: 10.1038/nm.4142
44. Kim W-G., Kang G-D., Kim HI., Han MJ., Kim D-H. *Bifidobacterium longum* IM55 y *Lactobacillus plantarum* IM76 alivian la rinitis alérgica en ratones al restaurar el desequilibrio Th2/Treg y la alteración de la microbiota intestinal. Benef Microbes. 2019;10(1):55–67. DOI: 10.3920/BM2017.0146
45. Dotterud CK., Storrø O., Johnsen R., Øien T. Probióticos en mujeres embarazadas para prevenir enfermedades alérgicas: un ensayo aleatorizado, doble ciego. Br J Dermatol. 2010;163(3):616–23. DOI: 10.1111/j.1365-2133.2010.09889.x
46. Enomoto T., Sowa M., Nishumori K., Shimazu S., Yoshida A., *et al*. Efectos de la suplementación con bifidobacterias en mujeres embarazadas y lactantes en la prevención del desarrollo de alergias en lactantes y en la microbiota fecal. Allergology international. 2014;63:575-585. DOI: 10.2332/allergolint.13-OA-0683
47. Schmidt RM., Laursen RP., Bruun S., Larnkjær A., Mølgaard C., Michaelsen KF., *et al*. Los probióticos en la infancia tardía reducen la incidencia de eccema: un ensayo controlado aleatorio.Pediatr Allergy Immunol. 2019;30(3):335–40. DOI: 10.1111/pai.13018
48. Del Giudice MM, Indolfi C, Capasso M, Maiello N, Decimo F, Ciprandi G, Ital J. Mezcla de bifidobacterias (*B longum* BB536, *B infantis* M-63, *B breve* M-16V) en el tratamiento de niños con rinitis alérgica estacional y asma intermitente. Pediatr. 2017;43:25. DOI: 10.1186/s13052-017-0340-5
49. Anania C., Di Marino VP., Olivero F., De Canditiis D., Brindisi G., Iannilli F., *et al*. Tratamiento con una mezcla probiótica que contiene *Bifidobacterium animalis* Subsp. *Lactis* BB12 y *Enterococcus faecium* L3 para la prevención de los síntomas de la rinitis alérgica en niños: un ensayo controlado aleatorizado. Nutrients. 2021;13(4):1315. DOI: 10.3390/nu13041315
50. Kang M-G., Han S-W., Kang H-R., Hong S-J., Kim D-H., Choi J-H. El probiótico NVP-1703 alivia la rinitis alérgica al inducir la expresión de IL-10: un ensayo clínico de cuatro semanas. Nutrients. 2020;12(5). DOI: 10.3390 / nu12051427.