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USE OF BIOTICS AS PROPHYLAXIS FOR NECROTIZING ENTEROCOLITIS IN PRETERM NEONATES

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Abstract:
Necrotizing enterocolitis in premature neonates is a disease that involves inflammation of the intestinal tissue, which leads to perforation of the intestinal wall or necrosis in the mucosa of the digestive tract. This pathological condition prevents the premature infant's body from retaining waste material, so bacteria and other pathogens can enter the bloodstream and cause life-threatening infections.
Objective: to systematize the suitable scientific evidence on the use of biotics as prophylaxis of Necrotizing Enterocolitis in preterm neonates.
Methodology: This study is a bibliographic review approached under a descriptive - explanatory design and with a qualitative approach, considering the following sources of information: Science Direct, PubMed, Scopus, Lilacs, Cochrane, Redalyc, SciELO and Proquest.
Results: Between strategies to consider to prevent the appearance of necrotizing enterocolitis in preterm neonates is to achieve a functional balance of the microbiotics or intestinal flora. This situation is possible thanks to the administration of probiotics, which are responsible for producing a beneficial effect on the host, and prebiotics, which have the ability to induce the growth of beneficial microorganisms.
Conclusions: Lactobacillus and Bifidobacterium are the probiotics with the greatest benefit and encouraging results in the prevention and control of severe necrotizing enterocolitis in preterm neonates; while galactooligosaccharides, fructooligosaccharides and oligosaccharides are the prebiotics found naturally in breast milk and contribute to this end.

Keywords: Necrotizing enterocolitis; preterm neonates; Biotics; probiotics; prebiotics; Prophylactic treatment.

INTRODUCTION:

The World Health Organization [WHO] (1), reports that preterm neonates are all babies who fail to fully develop within the uterus of the pregnant woman and that prior to 37 weeks of gestation they are born, requiring special care and permanent follow-up to prevent the number of complications to which they are significantly exposed. In addition, depending on the time of delivery, some organs and

systems tend to form incompletely, which considerably increases their morbidity and mortality rate (2).

Rodríguez et al. (3), states that the birth of preterm neonates does not have a defined cause, on the contrary, it is an event influenced by genetics and different medical aspects among which denote the following: infections or other discomforts that occur during fetal development; early induction of labour; caesarean section births and other chronic pathological conditions, such as diabetes and hypertension (4).

At present, although there have been notable advances in the care of preterm neonates, certain conditions such as: lack of maturity of the lungs, the difficulty involved in regulating their body temperature, poor food intake, slow weight gain and other inflammations of tissues or organs, configure a scenario of significant risk for the survival of babies (5,6).

According to the data presented in the report promoted by the Economic Commission for Latin America [ECLAC] (7), the rate of preterm neonates is between 5% and 18% of births worldwide, which represents the delivery of close to 15 million babies. Therefore, according to the WHO (8), this population group denotes having a high probability of developing a series of complications that lead to perinatal morbidity and mortality.

One of these complications is precisely necrotizing enterocolitis (NEC), referred to by Hachi et al. (9), as a disease of notable incidence and severity in premature babies, whose onset arises when the small or large intestine is inflamed or injured, which results in perforation of the intestinal wall or necrosis in the mucosa of the digestive tract, leading to an ischemic process of rapid and progressive development that prevents the infant's body from retaining waste material, allowing bacteria and other pathogens to enter the bloodstream and produce life-threatening infections (10).

Although necrotizing enterocolitis is a common condition in premature infants, infants with a body mass of less than 1500 grams or with a considerable stay in the neonatal intensive care unit [ICU] are also exposed to this pathology (11). This assertion is corroborated by Bonilla et al. (12), who report that preterm births with decreased birth weight show a higher incidence of cases, with a worldwide prevalence that affects a total of 1 to 4 per 1000 newborns; In addition, the mortality of this pathology borders 20% to 50% of registered cases and the population that manages to overcome the disease, are exposed to alterations in their subsequent physical growth and neuronal development.

This premise is corroborated by Adams et al. (13), who conclude that necrotizing enterocolitis is one of the pathological conditions with the greatest harmfulness and incidence in preterm neonates; with a prevalence that affects 7.7% of all cases that were admitted to neonatal ICUs worldwide; Additionally, it is reported that the vulnerability of this population group increases significantly, the earlier the gestational age at birth and the lower their body weight (14).

At the Latin American and Caribbean level, the prevalence of NEC is uncertain as a result of the paucity of studies presenting reliable and inconsistent data (15); however, in a recent report by Sandoval et al. (16), it is estimated that the level of incidence of the disease affects 7% to 10% of premature newborns who were admitted to neonatal ICUs, with a mortality rate ranging up to 30% of registered cases. In addition, according to Martínez et al. (17), approximately 13% of cases registered with this pathological condition are full-term babies and 5% of these cases show low birth weight, somewhat less than 1500 grams.

With regard to Ecuador, according to the report provided by the National Institute of Statistics and Censuses [INEC] (18), necrotizing enterocolitis is one of the main diseases that condition the survival and development of infants; In addition, for the year 2016, 67 deaths of preterm neonates were registered, which corresponds to 2.07% of mortality of a prevalence that borders on 7% of those born before 37 weeks of pregnancy (19). Of this total of patients diagnosed, between 20% and 40% will require complementary treatment that involves surgical intervention, a process that increases the probability of developing certain postoperative complications such as wound dehiscence, intestinal stenosis or obstruction, intra-abdominal abscesses and neurological morbidity that affects the psychomotor development of infants (20,21).

The etiology of NEC according to the data presented by Zozaya et al. (22), is multifactorial, being a disease associated with various pathological conditions, among the main risk factors linked to its

appearance, are the following: being a premature neonate, lack of maturity of the intestine, inadequate barrier of the intestinal mucosa, alterations of the microbiota, microbial dysbiosis, intrauterine growth retardation, limited circulatory stability at the level of the digestive tract, an early feeding process after childbirth and neonatal sepsis (23). Similarly, this condition can occur in full-term births, a situation that derives from hypoxia ischemia, hypertension, congenital heart disease and blood infections (24).

With regard to the symptoms associated with the development of NEC, they include the following clinical manifestations: bilious emesis, distension at the level of the abdomen, gastric waste, melena and a series of physiological situations that present abnormally, such as apnea, low heart pressure (bradycardia), abnormal or unstable blood pressure (hemodynamic alterations) and thermal instability (25,26).

Most preterm neonates born with low body weight manage to survive thanks to a series of special care and the use of certain medications duly prescribed by the respective professionals (27); However, with regard to the approach of patients with necrostic enterocolitis, therapeutic advances have been minimal, therefore, before birth, it is essential to act with extreme caution and emphasizing the respective analysis procedures, in order to diagnose this intestinal problem in a timely and early manner, because it is a condition that stands out for being aggressive and complex to stop (28,29).

However, Bifidobacteria is a microorganism that lives in the intestine of the neonate born by vaginal delivery and is beneficial for infants who are breastfed, because they are exposed early to the environment; on the other hand, babies born by cesarean section show a decrease in Bacteroides and Bifidobacterium, as a result of late exposure to the environment, which increases their vulnerability to greater colonization of opportunistic pathogens such as Enterococcus, Clostridium, Enterobacter and Klebsiella species (30,31).

In this sense, one of the efficient ways to prevent the onset of necrotizing enterocolitis and complications associated with pathological development is to add dietary supplements to breastfeeding (29). These aggregates, called biotics, are made up of probiotics and prebiotics, which are characterized by having bacteria and/or yeasts beneficial to the intestinal microbial and help protect the immature intestine against inflammation or other injuries, which greatly reduces the risk of suffering from this disease and the morbidity and mortality associated with it (32).

Therefore, they are living organisms that significantly benefit the intestinal flora, by expanding saprophytic flora and contributing to the inhibition of the increase of pathogenic bacteria (33). Its use as prophylaxis denotes in medical practice, since according to scientific evidence it reduces necrotizing enterocolitis in premature neonates (29).

The social impact of this study focuses on providing clear and concise information on the use of certain biotics that contribute to the prevention of the disease, reducing the risk in the neonate, intervention time and high treatment costs. Therefore, the central objective arises to systematize the suitable scientific evidence on the use of biotics as prophylaxis of Necrotizing Enterocolitis in preterm neonates.

METHODS:

A narrative bibliographic review was carried out, under a qualitative approach, based on various theoretical foundations collected from different sources of scientific information duly validated, which were referenced by the Mendeley Data Manager, thereby providing considerable academic probity to the research.

The bibliographic review was carried out under a descriptive design, since it was exposed in a detailed and duly supported manner, the different aspects related to the effects, functionality and application criteria applied in biotics, when used as prophylactic therapy of necrotizing enterocolitis in preterm neonates.

The sources of information that were considered for the development of this narrative bibliographic review were the following: PubMed, Scopus, Lilacs, Cochrane, Redalyc, SciELO and the databases of the Catholic University of Cuenca. The search for research published since 2018, in English or Spanish that supports the topic addressed, was carried out in the course of March 2023.

DEVELOPMENT:

1. NECROTIZING ENTEROCOLITIS IN PRETERM NEONATES

NEC in preterm neonates is referred to by Hachi et al. (9) as a serious pathological condition that affects premature babies and leads to injury of the small or large intestine of their anatomy, which often leads to severe damage and can even kill the tissue of their colon. According to González et al. (10), this disease frequently affects newborns who remain for a certain period of time in the neonatal ICU, who are mostly characterized by having a weight equal to or less than 1500 grams.

The injury or inflammation produced by this pathology can lead to the death of intestinal tissue or perforation of the intestinal wall, which is why the neonate's body loses the ability to retain fecal waste, allowing the different bacteria and other microorganisms that are located in said waste, to reach the bloodstream and promote an infectious scenario of risk for the survival of the neonate (10).

Regarding the **etiology** of necrotizing enterocolitis in preterm neonates, according to Bernuy et al. (11), the cause that gives rise to this pathological condition is unknown for sure, however several studies agree that an insufficient supply of blood and oxygen to the intestinal tissues is directly associated with its development, allowing the bacteria contained in the food that the baby ingests to damage this set of cells to the point of causing their death and causing a serious infection in the abdomen of the newborn.

Bonilla et al. (12), state that the main **clinical manifestations** that lead to the development of this pathological condition are: the belly is sensitive to feel pain when palpated and tends to be red or edematized; the neonate shows difficulty in ingesting food and those that reach the stomach remain for a while out of the ordinary; there are problems to defecate and at the time of doing so, The stools are dark, bloody, or diarrhea-like (34).

In addition, the baby tends to be drowsy, tired and less active; its temperature is unstable, with a tendency to fall for no reason; frequently vomiting bilious; has difficulty breathing, accompanied by an irregular heart rhythm either low or high (12,35).

Although the manifestations of the disease vary from one infant to another, some of the symptoms are a consequence of other digestive conditions; Similarly, necrotizing enterocolitis in preterm neonates is caused by ischemic lesions, bacterial colonization or enteral feeding (16). According to Cochran (25), when witnessing any of the aforementioned symptoms, it is essential to make the timely diagnosis of the disease, which can be carried out by means of an x-ray of the baby's abdomen or the practice of an ultrasound.

The confirmation of the disease in the body of a baby, leads to an unlikely distribution of gases in the intestine, showing in the intestinal wall in the form of a bubble (36). In addition, in critically ill patients, air escapes from the intestine, being directed to the abdominal cavity, so a health professional may resort to inserting a needle into the belly and proceed with the extraction of fluid in order to determine if it is perforated or not (37).

Once the presence of the disease has been diagnosed by chance, it is essential to start treatment immediately. According to Guzmán et al. (38), among the alternatives to consider are the following: stopping any intake temporarily; insert a tube through the nose or mouth towards the stomach, through which air or liquid will be extracted as a drain; keeping the infant nourished through intravenous administration of liquid substances; giving certain antibiotics; provide ongoing follow-up with physical examinations or x-rays of the abdomen; consider possible surgery in case of complications (39).

Once the infant's body responds effectively to the selected treatment, feeding can return to normal in an estimated time of one to two weeks. In the first instance, breast milk should be used, as it is an easy to digest substance, promotes the growth of bacteria that are healthy for the intestine and provides the nutrients, proteins and antibodies required to stimulate the baby's immunity (40).

1.1. Function of intestinal flora and necrotizing enterocolitis

Native microorganisms are those acquired by the organism of the human being, between the stage of birth and the first twelve months of life; while transient bacteria are ingested permanently through the different foods and / or substances that are part of the nutrition of an individual. In this sense, the

intestine, which is part of the anatomy of the human being, is referred to by Rodríguez & Saavedra (41) as the natural scenario where these agents interact dynamically and whose survival implies adaptation to mucosal surfaces.

In this sense, according to Merino et al. (42), the microbiota or intestinal flora includes the entire microbial ecosystem housed in the human intestine, this includes native bacteria that permanently establish themselves in the gastrointestinal tract and those that circulate transiently along the digestive tract. This set of microorganisms establishes an interaction of mutual help or symbiosis with the host. Among the main functions of the intestinal flora, they denote the following: it is the component responsible for providing protection to the human organism, against any infection or other harmful impact that could produce any of the bacteria that inhabit your intestine; facilitate the digestion of inferred food products and allow foods rich in vitamins B and K to be properly synthesized, contributing to a correct strengthening of the immune system (43).

2. USE OF BIOTICS AS PROPHYLAXIS OF NECROTIZING ENTEROCOLITIS IN PRETERM NEONATES.

Biotic agents include a series of microorganisms that have certain characteristics or properties that can directly contribute to preventing a number of conditions on the human organism and/or maintaining its state of health (44). In the case of necrotizing enterocolitis that affects preterm neonates, the use of *probiotics and prebiotics is differentiated as reliable alternatives.*

Probiotics are referred to by González & Muñoz (45), as the set of foods or food supplements that provide a series of live microorganisms that directly contribute to maintaining or improving the state of the intestinal microbiota that is part of the organism of the preterm neonate; in other words, they are different agents that supplied in specific quantities bring with them a series of direct benefits for the health status of the infant, being able to prevent or control certain gastrointestinal conditions.

Barclay et al. (46), states that probiotic resources are found in substances such as yogurt and sauerkraut that derive from the process involved in the fermentation of cabbage leaves. However, constant advances in technology and medicine currently allow these microorganisms to be administered in the form of liquid, powder or capsules, either as part of an individual's functional diet or a supplement that helps meet the nutritional needs of their body, bringing with it a series of benefits in the health status of the host (47).

Probiotics are characterized by being non-pathogenic agents, that is, their administration is not harmful to human health. The different species and species that these microorganisms present are of human origin and have the ability to survive by moving along the entire route of the gastrointestinal tract (44). The properties of these agents are effective in preventing or treating a series of acute pathological conditions at the digestive level and chronic intestinal and hepatic diseases, as they contribute to the host's immune system and intestinal homeostasis, and even have the ability to modulate the microbiota of the intestine (48).

Prebiotics contemplate a series of food resources that generally nourish the intestinal flora of the human being and contribute to achieving a better balance of all the microorganisms found in this microbial ecosystem. According to Bernal et al. (49), these functional properties are found in products such as bananas, garlic, whole grains, soybeans, artichokes and other green vegetables; In addition, today they are also available in food supplements with high fiber content, which must be administered according to a medical prescription.

Currently, according to the report addressed by Castañeda (43), the prebiotics with the greatest approach are inulin, lactulose, oligofructose, oligosaccharides contained in breast milk and fructooligosaccharides. Most of these elements are found naturally in products such as onions, oats, potatoes, artichokes, leeks, honey, legumes and other green products; In addition, certain manufacturers within the pharmaceutical area can add them so that certain foods obtain concrete benefits.

The level of efficiency of the administration of a probiotic or prebiotic depends directly on the strain or type of resource and the amount of dose delivered to the host; However, although these microorganisms are tolerated by an individual's body, they sometimes cause certain adverse effects that condition their vital functions (45).

2.1. Prophylactic treatment with probiotics, protective and adverse effects

According to the study conducted by Sharif et al. (50), neonates born in an average time of eight weeks prior to the end of gestation and a body weight of less than 1.5 kg are the population group at highest risk for developing necrotizing enterocolitis. Given this reality, the administration of probiotics significantly reduced the probability that these newborns suffer from this pathological condition; In the same way, they help prevent the infant mortality rate due to some complication that entails the development of this pathology.

This intervention consists of complementing breastfeeding, with the administration of food supplements whose compounds contain certain microorganisms or yeasts that are of remarkable benefits for the organism of the newborn. According to the study proposed by Gutiérrez et al. (51), the most reliable probiotic against this disease of neonates is Lactobacillus from the casei rhamnosus strain, since its properties allowed to reduce the severity of necrotizing enterocolitis and achieve late mortality, in children who did not exceed three years of age; In addition, it should be mentioned that this resource did not generate any adverse effect on the treated infants, which could be determined by comparing several medical records.

These data agree with those stated by Rojas et al. (52), who report that the isolated strain of the probiotic Lactobacillus reuteri is an element that survived in the digestive tract and complemented breastfeeding safely. Indrio et al.(53), affirm that this resource produces reuterin, an antimicrobial substance that helps in the control and reduction of infections or inflammations at the gastrointestinal level, which greatly reduces the stay in a health unit.

Likewise, the data provided by Baucells et al. (54), establish that the probiotic Lactobacillus reuteri administered from the third day of birth of a neonate, until 36 weeks of gestational age, in a single daily dose, significantly reduce the level of cases diagnosed with necrotizing enterocolitis, without presenting any adverse effects; Likewise, the use of these resources largely avoided the idea of resorting to surgical interventions or surgery and there were no lethal patients, that is, the mortality rate also decreased.

In the results obtained by Chi et al. (55), it is concluded that Lactobacillus and Bifidobacterium are probiotics that administered in combination also contribute significantly in reducing the level of incidence of cases of NEC in preterm infants weighing less than 1500 grams. This combination is the most reliable when it comes to reducing infant mortality and did not bring side or adverse effects in infants, however, the doses and duration of treatment varies depending on the organism of each neonate.

In the study carried out by Suárez & Solís (32), it is concluded that the combined prophylactic treatment between the probiotics Lactobacillus + Bifidobacterium, turned out to be an extremely effective alternative to decrease the incidence of cases of NEC in premature children and the mortality rate of this pathological condition, without presenting adverse effects in the short or long term.

Finally, several of the studies addressed agree that the properties of these probiotic resources allow them to easily adhere to the intestinal mucosa, exclude and inhibit pathogenic microorganisms, control their growth, produce antimicrobial substances and strengthen the immune system of the newborn, configuring a favorable scenario for the well-being and survival of neonates.

2.2. Prophylactic treatment with prebiotics, protective and adverse effects

Prophylactic treatment with prebiotics, in the face of necrotizing enterocolitis in preterm neonates, consists of modulating the intestinal microbiota of the newborn through the intake of different functional foods such as carbohydrates, which have the ability to encourage the growth and development of microorganisms that are beneficial for the health status of the infant (45).

According to the study carried out by Castro et al. (49), prebiotics contemplate a series of oligo and polysaccharide substances that have certain properties to stimulate the intestinal flora and especially the colon area, allowing the fermentation of Lactobacillus and Bifidum, microorganisms that promote the simultaneous production of short-chain fatty acids, which directly contribute to the reduction of the pH of the digestive tract and the management or control of those Ecological niches where different bacterial communities are housed, which are harmful to the infant's organism.

In this regard, according to the analysis proposed by Murphy et al. (26), among the protective effects involved in the administration of prebiotic elements, they denote the considerable reduction in the time that bacteria occupy to transit through the intestinal tract, increasing the fecal bolus and the frequency with which infants perform their respective stools. This is consistent with what was stated by Gutiérrez et al. (33), who report that treatment with these food resources favors the colonization of beneficial microorganisms to control any infection or inflammation that may have appeared along the gastrointestinal tract.

In this regard, according to Duffield & Clarke (56), the mother's milk is one of the substances that stands out for its high content of prebiotics, among which are precisely galactooligosaccharics and fructooligosaccharides, food resources that significantly favor balancing the intestinal flora of lactating neonates. Nolan et al. (57), affirm that breastfeeding contributes with a varied content of natural oligosaccharides, everything depends on the organism of each female and the stage of development that the infant faces, however, they are always a source of probiotics called bifidobacteria.

In this sense, according to the report promoted by Castro et al. (49), exclusive breastfeeding is part of the most effective prebiotic treatment to reduce the risk of suffering any alteration in the balance of the intestinal flora of the newborn, therefore, the probability of developing necrotizing enterocolitis; Similarly, some clinical studies agree that the oligosaccharides contained in the mother's milk contribute to the production of safe probiotics to prevent, control or treat this pathological condition in very premature children.

According to the results presented by Chi et al. (55), infants who are born very prematurely, are characterized by a lower load of probiotic resources that favor the balance of their intestinal flora, on the contrary, the presence of pathogenic microorganisms is greater, a situation that derives as a result of fasting or the administration of certain antibiotics. In this scenario, breast milk contains oligosaccharides, prebiotics that favor the growth of non-pathogenic probiotic resources, such as lactobacilli and bifidobacteria, which balance the gut microbiota and contribute to the strengthening of the mucosal barrier (56).

In the study led by Nolan et al. (57), it is concluded that synthetic oligosaccharides contained in food supplements such as formula milk is a prebiotic that encourages the growth and balance of intestinal flora in a similar way to infant newborns who are fed only with their mother's milk; however, no evidence was found to show the reliability of its administration in preventing NEC and/or reducing the mortality rate associated with complications of this pathological condition.

Finally, it should be mentioned that, although there are no adverse effects of consideration after the use of these prebiotics, the body of the newborn may present certain conditions of lesser severity such as: mild colic, gas, nausea, constipation and diarrhea. In the event of such effects, the administration of these substances should be discontinued immediately and treatment should be carried out to counteract them as soon as possible (49).

2.3. Functions in the intestinal flora and application criteria according to the characteristics of the neonate

The intestinal microbiotic is a fundamental component in the state of health of the human being, it houses a number of bacteria that colonize in the walls of the intestine or usually transit throughout the digestive tract. Its functions are focused on preventing pathogens from colonizing and giving way to infections or other pathological conditions; regulate intestinal transit; produce vitamins and other components that contribute to the growth of the infant; and contribute to the immune system maturing correctly.

Under this premise, the NEC contemplates an intestinal inflammation, which can lead to severe damage or death of the colon tissue. The appearance of this pathological condition is associated with the colonization of different dangerous microorganisms or the growth of other bacteria in certain parts of the digestive tract where their accommodation is unusual; hinting at the presence of a problem in the functionality of the microbiota or intestinal flora.

Prophylactic treatment by means of **probiotics**, entails the following **functions** in the intestinal flora: increases the production of short-chain antimicrobial elements, which counteract harmful microorganisms or the generation of harmful toxins for the newborn's organism; lowers the pH of the digestive tract, achieving a favorable scenario for the growth and colonization of non-pathogenic bacteria; promotes greater resistance to colonization of pathogens and strengthens the autoimmune system.

With regard to the criteria for the **application of** probiotic elements, according to the characteristics of the neonate, the following specifications should be considered:

a) Probiotics should be administered as the first treatment alternative in neonates born before 32 weeks of the process that entails pregnancy and / or who weigh less than 1,500 grams; In addition, they require continuous or permanent monitoring, in order to timely identify any adverse effects or complications in the newborn's body.
b) In children weighing less than 1000 grams, it is recommended to use the combination of the probiotics Lactobacillus and Bifidobacterium, in a daily and single dose of 3x109 CFU, starting with 1.5x108 until reaching the enteral dose of 50 ml / kg / day.
c) The administration of these probiotics should begin during the first 7 days of life of the neonate, when enteral feeding begins and be maintained at least during the 35 weeks postgestational or depending on the case addressed, until discharge.
d) No probiotic supplement should be given to neonates presenting with acute illness such as sepsis or perinatal asphyxia.

On the contrary, with regard to prophylactic treatment by means of **prebiotics**, it entails the following **functions** in the intestinal flora: it helps to control the spread of pathogenic microorganisms, allows the microorganisms housed in this environment to remain stable and not lend themselves to any harmful mutation, nourishes the microbiota and improves the balance of all bacteria, configuring a favorable scenario to prevent alterations that lead to gastrointestinal diseases such as necrotizing enterocolitis.

With regard to the criteria for the **application of** prebiotic elements, according to the characteristics of the neonate, the following specifications should be considered:

a) Prebiotics should be administered to preterm infants weighing less than 1,500 grams; It is not recommended in newborns weighing less than 1000 grams.
b) Attention should be paid to manifestations such as the appearance of colic, gas, nausea, constipation and diarrhea, as these are conditions for which the administration of the prebiotic should be discontinued.
c) The most recommended prebiotics are galactooligosaccharics, fructooligosaccharides and oligosaccharides, contained mostly naturally in the mother's milk, which significantly favors balancing the intestinal flora of lactating neonates.
d) Administration can begin once postgestational life begins, and can be maintained throughout exclusive breastfeeding.

Finally, many food resources of the probiotic type are administered together with a prebiotic, a combination that gives rise to a component called symbiotic, which has both effects in a single product.

CONCLUSIONS:

The intestinal flora is the component responsible for defending the body from different pathogenic microorganisms that can lead to certain pathological conditions, contribute to the proper functioning of the digestive system and affect the production and / or absorption of vitamins and minerals.

One of the intestinal conditions with the highest incidence in preterm neonates is necrotizing enterocolitis. Among the strategies to be considered to avoid the appearance of NEC in preterm neonates, is to achieve a functional balance of the microbiotic or intestinal flora. This situation is possible thanks to the administration of probiotics, which are responsible for producing a beneficial effect on the host and prebiotics, which have the ability to induce the growth of beneficial microorganisms.

All the studies addressed agree that it is advisable to use probiotic resources in preterm infants, as it is an intervention that contributes significantly to reducing the mortality rate to half of all deceased newborns and reducing the number of cases diagnosed with severe NEC by up to two thirds.

Lactobacillus and Bifidobacterium are the probiotics with the greatest benefit and encouraging results in the prevention and control of severe NEC in preterm neonates. Galactooligosaccharics, fructooligosaccharides and oligosaccharides are the prebiotics that are found naturally in breast milk and that significantly favor achieving a correct balance in the intestinal flora of the neonate.

Conflict of interest:

There were no conflicts of any kind that could condition its development.

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REFERENCES:

1. World Health Organization [WHO]. Premature babies: stories of six mothers [Internet]. Publications. 2019 [cited 2023 Apr 16]. Available from: https://www 3.paho .org/hq/index.php?option=com_content&view=article&id=15581:by-a-appropriate-attention-in-the-just-time-and-in-the-right-place&Itemid=0&lang=en#gsc.tab=0
2. Galvin M. If Your Baby Is Born Premature [Internet]. KidsHealth. 2021 [cited 2023 Apr 16]. Available from: https://kidshealth.org/es/parents/preemies.html
3. Rodrigues A, Coeli B, Barreto V, Rodrigues A, Vasconcelos E, Rodrigues A. Profile of at-risk infants related to thermoregulation in a Neonatal Intensive Care Unit. Nursing Glob [Internet]. 2021 Feb 5;20(1):59–97. Available from: https://revistas.um.es/eglobal/article/view/414201
4. Ota A. Neonatal management of prematurity: advances in Peru. Rev Peru Ginecol and Obstet [Internet]. 2018 Sep;64(3):415–22. Available from: http://www.scielo .org.pe/scielo.php ?script=sci_arttext&pid=S2304-51322018000300015
5. Chávez T, Byard D, Amaya C. Late preterm infant: incidence and early neonatal morbidity. Arch Venez Pueric Pediatr [Internet]. 2019;72(2):59–67. Available from: http://www.redalyc .org/articulo.oa?id=367937038005
6. Geronimo N. Preterm birth since live birth records in Colombia, period 2008 – 2017. Rev Médica Risaralda [Internet]. 2020 Dec;26(2). Available from: http://www.scielo.org. co/scielo. php?pid=S0122-06672020000200138&scrypt=sci_abstract &tlng=en
7. Economic Commission for Latin America [ECLAC]. Population notes [Internet]. Premature births. 2021 [cited 2023 Apr 16]. p. 11–37. Available from: https://www.cepal.org /es/publicaciones/41954-notas-poblacion-vol-44-ndeg-104
8. World Health Organization [WHO]. 17 November, Prematurity Day: providing care is a right - PAHO/WHO | Pan American Health Organization [Internet]. News. 2020 [cited 2023 Apr 16].

p. 3. Available from: https://www.paho.org/es/noticias/17-11-2020-17-noviembre-dia-prematuro-brindar-atencion-cuidado-es-derecho
9. Hachi H, Chichande R, Montjoy W, Jaramillo M, Baños K. Necrotizing enterocolitis. Gastrointestinal emergency of the newborn. Rev Pertinencea Academic [Internet]. 2022;6(2):1–12. Available from: https://revistas.utb.edu.ec/index.php/rpa/article/download/2652/2263
10. González P, Escudero S, Gutiérrez F, González A. Use of probiotics in the prevention of necrotizing enterocolitis. Rev Electronic Pediatrics [Internet]. 2021;28(3):29–35. Available from: https://www.revistapediatria.cl/volumenes/2021/vol18num3/pdf/USO PROBIOTICS PREVE-NTION NECROTIZING ENTEROCOLITIS.pdf
11. Bernuy S, Loor N, Ruíz G, Cevallos D. Clinical characterization and morbimpostsurgical orthology of the NB with necrotizing enterocolitis. Rev J Am Heal [Internet]. 2021;4(2):34–44. Available from: https://jah-journal.com/index.php/jah/article/view/96
12. Bonilla E, Ramírez L, Rojas P, Zuñiga B. Necrotizing enterocolitis. Rev Med Leg Costa Rica [Internet]. 2020;37(2):63–70. Available from: https://www.scielo. sa.cr/scielo.php? script=sci_ arttext&pid=S1409-00152020000200063
13. Adams M, Bassler D, Darlow BA, Lui K, Reichman B, Hakansson S, et al. Preventive strategies and factors associated with surgically treated necrotising enterocolitis in extremely preterm infants: an international unit survey linked with retrospective cohort data analysis. BMJ Open [Internet]. 2019 Oct 14;9(10):e031086. Available from: https://bmjopen.bmj. com/lookup/doi/10.1136/bmjopen-2019-031086
14. Denning N, Prince J. Neonatal intestinal dysbiosis in necrotizing enterocolitis. Mol Med [Internet]. 2018 ofC 15;24(1):4. Available from: https://molmed.biomedcentral .com/articles /10.1186/s10020-018-0002-0
15. Rodríguez A, Golombek S, Siben S. Necrotizing enterocolitis in the Ibero-American network: incidence, timing of presentation and mortality [Internet]. Presentación of posters. 2020 [cited 2023 Apr 16]. p. 1–10. Available from: https://www.siben. net/images/htmleditor /files/pantalla_c.pdf
16. Sandoval A, Cofré F, Hernández M, Izquierdo G, Labraña Y, Reyes A, et al. Clinical-epidemiological characterization of neonatal necrotizing enterocolitis from seven public hospitals. Rev Chil infectology [Internet]. 2020 Dec;37(6):667–74. Available from: http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S071610182020000600667&lng=en&nrm=iso&tlng=en
17. Martinez D, Jaimes M, Vargas F, Chaparro D, Manrique E. Necrotizing enterocolitis: sociodemographic, clinical and histopathological neonatal findings in a series of neonatal autopsies. Rev la Fac Ciencias la Salud [Internet]. 2020;23(1):35–42. Available from: https://docs.bvsalud.org/biblioref/2020/04/1087359/3682.pdf
18. National Institute of Statistics and Censuses [INEC]. Statistical Compendium [Internet]. 2018 [cited 2023 Apr 16]. Available from: https://www.ecuadorencifras.gob.ec/compendio-estadistico-2016/
19. Lapo N, Vasquez F. Necrotizing enterocolitis [Internet]. Presentation of two clinical cases. 2018 [cited 2023 Apr 16]. Available from: http://revistabionatura.com/2018.03.02.10-1.html
20. Ministry of Public Health of Ecuador [MSP]. Deaths and mortality profile of the National Health System [Internet]. Facts and figures. 2018 [cited 2023 Apr 16]. Available from: https://public.tableau.com/profile/darwin5248#!/vizhome/defunciones2016/Historia1?publish=yes.
21. Escalona P. Enterocolitis Necrotisante. Rev Médica Sinerg [Internet]. 2018;3(4):3–8. Available from: https://www.medigraphic.com/pdfs/sinergia/rms-2018/rms184a.pdf
22. Zozaya C, Avila A, Somoza I, García F, Encinas J. Prevention, diagnosis and treatment of necrotizing enterocolitisand in newborns less than 32 weeks at birth in Spain. Rev An Pediatrics [Internet]. 2020;93(3):161–9. Available from: https://www.analesdepediatria.org/es-prevencion-diagnostico-tratamiento-enterocolitis-necrotizante-articulo-S169540332030031X
23. Casal B, García M, Novoa A, Somoza A, Dargallo T. Appendicitis as a cause of acute abdomen

in neonatal stage. About a case. An Sist Sanit Navar [Internet]. 2018 Aug 29;41(2):249–53. Available from: https://recyt.fecyt.es/index.php/ASSN/article/view/62586/40715
24. Demestre G, Raspall T. Necrotizing enterocolitis [Internet]. Spanish Association of Pediatrics. 2019 [cited 2023 Apr 16]. p. 405–11. Available from: https://www.aeped.es /sites/ default/files/documentos/42.pdf
25. Cochran W. Enteroconecrotizing litis [Internet]. Gastrointestinal and liver problems newborn. 2021 [cited 2023 Apr 16]. Available from: https://www.msdmanuals.com/es/hogar/salud-infantil/problemas-gastrointestinales-gi-y-hepáticos-en-recién-nacidos/enterocolitis-necrotizante-ecn
26. Murphy K, Ross P, Ryan A, Dempsey E, Stanton C. Probiotics, Prebiotics, and Synbiotics for the Prevention of Necrotizing Enterocolitis. Front Nutr [Internet]. 2021 Sep 7;8(12):23–31. Available from: https://www.frontiersin.org/articlen/10.3389/fnut.2021.667188/full
27. World Health Organization [WHO]. Preterm Birth [Internet]. Facts and figures. 2022 [cited 2023 Apr 16]. Available from: https://www.who.int/es/news-room/fact-sheets/detail/preterm-birth#:~:text=En alls countries%2C the,18%25 of births.
28. Hakan O, Demirezen S, Demir M. Necrotizing enterocolitis: retrospective analysis of 1428 preterm infants in a level III neonatal intensive care unit over a period of four toYears. Arch Argent Pediatr [Internet]. 2020 Dec 1;118(6):405–10. Available from: https://www.sap.org.ar/docs/publicaciones/archivosarg/2020/v118n6a09.pdf
29. Sharif S, Meader N, Oddie S, Rojas M, McGuire W. Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants. Cochrane Database Syst Rev [Internet]. 2020 Oct 15;2020(10). Available from: http://doi.wiley.com/10. 1002/14651858. CD005496.pub5
30. National Institute of Health [NIH]. Probiotics [Internet]. Dietary Supplement Fact Sheets. 2020 [cited 2023 Apr 16]. Available from: https://ods.od.nih.gov/factsheets/Probiotics-DatosEn Espanol/
31. Álvarez G, Guarner F, Requena T, Marcos A. Diet and microbiota. Impact on health. Nutr Hosp [Internet]. 2018 Sep 7;35(6). Available from: http://revista.nutricionhospitalaria.net/ index.php/nh/article/view/2280
32. Suárez M, Solís G. Probiotics and necrotizing enterocolitis: where are we in 2021? Rev Evidencias en Pediatría [Internet]. 2021;17(3). Available from: https:// evidenciasenpediatria.es/articulo/7889/probioticos-y-enterocolitis-necrotizante-donde-estamos-en-2021
33. Gutiérrez C, Bustos L, Caniulao K, Taito K, Gallegos Y. Probiotic intervention for the prevention of necrotizing enterocolitis in extreme preterm infants less than 1500 grams or 32 weeks. Arch Argent Pediatr [Internet]. 2021 Jun 1;119(3):185–91. Available from: https:// www.sap.org.ar/docs/publicaciones/archivosarg/2021/v119n3a08.pdf
34. Tamayo M, Arango M, Tamayo C. Pathophysiology and risk factors for the development of necrotizing enterocolitis in neonates smaller than 1,500 g. Rev Iatreia [Internet]. 2019;19(4):108–17. Available from: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0121-07932006000400003
35. Dirnberger D. Necrotizing enterocolitis [Internet]. Nemours Kids Health. 2021. Available from: https://kidshealth.org/es/parents/nec.html
36. Pantoja S, Chamorro M. Scoliosis in children and adolescents. Rev Médica Clínica Las Condes [Internet]. 2019 Jan;26(1):99–108. Available from: https://linkinghub. elsevier.com/retrieve/pii/S0716864015000164
37. Bracho E, Torrecilla M, Zalles C, Ibarra D, Fernández E, Dávila R. Prognostic factors for mortality in neonates with necrotizing enterocolitis. Cir Cir [Internet]. 2019 Jul;83(4):286–91. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0009741115000882
38. Guzmán J, Cabañas M, Ruíz D. Prevention of necrotizing enterocolitis in the newborn. Rev An Pediatrics Contin [Internet]. 2020;10(5):295–7. Available from: https://www.elsevier.es/es-revista-anales-pediatria-continuada-51-articulo-prevencion-enterocolitis-necrotizante-el-recien-S1696281812701026

39. Martinez D, Sanabria J, Jiménez F, Chaparro D, Manrique E. Necrotizing enterocolitis: sociodemographic, clinical and histopathological findings in a series of neonatal autopsies. MedUNAB [Internet]. 2020 Mar 31;23(1):35–42. Available from: https://revistas. unab.edu.co/ index.php/medunab/article/view/3682
40. Bracho E, Torrecilla M, Zalles C, Ibarra D, Fernández E, Dávila R. Prognostic factors for mortality in neonates with necrotizing enterocolitis. Cir Cir [Internet]. 2020 Jul;83(4):286–91. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0009741115000882
41. Rodriguez M, Saavedra N. Intestinal microbiota and modulation of adipose tissue in the pathogenesis of obesity. Rev Arch Latinoam Nutr [Internet]. 2022;72(2):100–8. Available from: http://ve.scielo.org/scielo.php?script=sci_arttext&pid=S0004-06222022000200100
42. Merino J, Taracena S, Díaz E, Rodríguez F. Intestinal microbiota: "the forgotten organ." Acta médica Grup Ángeles [Internet]. 2021;19(1). Available from: https://www.scielo.org. mx/ scielo.php?pid=S1870-72032021000100092&script=sci_arttext
43. Castañeda C. Intestinal microbiota and mental behavior disorders. Rev Cubana Pediatr [Internet]. 2020;92(2):106–15. Available from: http://scielo.sld.cu/ scielo.php?script=sci_ arttext&pid= S0034-75312020000200016
44. Perez S. Resources Biotic resources in the care of the disease. Rev científica Investig Reg [Internet]. 2019;39(1):33–54. Available from: https://pesquisa. bvsalud.org/portal/ resource/ pt/biblio-947721
45. González J, Muñoz M. ProbióTicos and necrotizing enterocolitis of prematurity; to NEC or not to NEC?, this is the question. Rev Nutr Hosp [Internet]. 2019;28(6):2115–23. Available from: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S0212-16112013000600042
46. Barclay A, Stenson B, Simpson J, Weaver L, Wilson D. Probiotics for necrotizing enterocolitis: a systematic review. Pediatr Gastroenterol Nutr [Internet]. 2019;8(45):569–75. Available from: https://scielo.isciii.es/scielo.php?script=sci_nlinks&ref=3703416&pid=S0212-1611201300060004200017&lng=es
47. Szajewska H, Guandalini S, Morelli L, Van Goudoever J, Walker A. Effect of Bifidobacterium animalis subsp lactis supplementation in preterm infants: a systematic review of randomized controlled trials. Rev Pediatr Gastroenterol Nutr [Internet]. 2020;8(51):203–9. Available from: https://www.sciencedirect.com/science/article/pii/S0261561411001579
48. Rappaccioli R, Zaror V, Herrera S. Probiotics: challenges, review and scope. Rev Medica Sinerg [Internet]. 2021 Jun 1;6(6):e686. Available from: https://revistamedicasinergia. com/index.php/ rms/article/view/686
49. Castro C, Díaz C, Gutiérrez C. Probiotics and prebiotics in plant-based matrices: Advances in the development of fruit beverages. Rev Chil Nutr [internet]. 2019;44(4):383–92. Available from: https://www.scielo.cl/scielo.php?script=sci_arttext&pid=S071775182017000400383&lng=en&nrm=iso&tlng=en
50. Sharif S, Meader N, Oddie S, Rojas M. Probiotics for preventing necrotizing enterocolitis in Very premature or very low birth weight infants. Cochrane Database Syst Rev [Internet]. 2020;10(8). Available from: https://www.cochrane.org/es/CD005496/NEONATAL_probioticos-para-la-prevencion-de-la-enterocolitis-necrotizante-en-recien-nacidos-muy-prematuros-o-de
51. Escáratea C, Gutiérrez M, Bustos L, Caniulao K, Taito C, Gallegos Y, et al. Probiotic intervention for the prevention of necrotizing enterocolitis in extreme preterm infants less than 1500 grams or 32 weeks. Rev Arch Argent Pediatr [Internet]. 2021;119(3):185–91. Available from: https://www.sap.org.ar/docs/publicaciones/archivosarg/2021/v119n3a08.pdf
52. Rojas M, Lozano J, Rojas M, Rodriguez V, Rondon M. Prophylactic probiotics to prevent death and nosocomial infection in preterm infants. Rev Pediatr. 2020;130(5):113–20.
53. Flavia M, Riezzo G, Raimondi F, Bisceglia M, Cavallo L, Francavilla R. The Effects of Probiotics on Feeding Tolerance, Bowel Habits, and Gastrointestinal Motility in Preterm Newborns. J Pediatric. 2019;152(6):801–6.
54. James B, Mercadal M, Tenesor A, Figueras J. Probiotic associations for the prevention of necrotizing enterocolitis and the reduction of late sepsis and neonatal mortality in preterm

newborns of less than 1,500g: a rsystematic vision. Rev An Pediatrics [Internet]. 2020;85(5):247–55. Available from: https://www.analesdepediatria.org/es-asociaciones-probioticos-prevencion-enterocolitis-necrotizante-articulo-S1695403315004002

55. Chi C, Li C, Buys N, Wang W, Yin C, Sun J. Effects of Probiotics in Preterm Infants: A Network Meta-analysis. Rev Pediatr. 2021;174(1).
56. Duffield S, Clarke P. Current use of probiotics to prevent necrotising enterocolitis. Arch Dis Child - Fetal Neonatal Ed [Internet]. 2019 Mar;104(2):F228–F228. Available from: https://fn.bmj.com/lookup/doi/10.1136/archdischild-2018-316199
57. Nolan LS, Rimer J, Good M. The Role of Human Milk Oligosaccharides and Probiotics on the Neonatal Microbiome and Risk of Necrotizing Enterocolitis: A Narrative Review. Nutrients [Internet]. 2020 Oct 6;12(10):3052. Available from: https://www.mdpi.com/2072-6643/12/10/3052