



## Mikrobiyata

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## Mikrobiyomlar ve Neonatoloji

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*Mikropsuz değil, dost mikrobiyomlu ortam yaratarak, biyolojik çevreyi fizyolojik olarak gastro-intestinal yapıyı sağlamak ile patolojik flora arasındaki farklılıklar tanımlanmalıdır. NEK (Nekrotizan Enterokolit) önemi ile prematüre mortalite karşılaştırılması, başka nedenler olduğundan dolayı, tek sebep ve sonuç ilintisi kurulması, zayıf bir yaklaşım olmaktadır.*

**M**ikroplar, temel olarak “Mikrobiyomlar” bizim ile aynı evreni, aynı ortamı paylaşan ve birlikteliğimizi yadsınmayacağımız olduğuna göre, patolojik flora ile karşılaştırma yapılması gereklidir. Literatür yaklaşımlarında farklı kavramların istatistikte konu edilmesi ile net doğru tam oraya konulamamaktadır.

Beslenme ötesinde Neonatoloji de ilk flora oluşması açısından Mikrobiyomlar önemlidir. Burada fizyolojinin oluşması kavramında ve anlamında konuyu ele almak daha gerçekçi ve doğru olacaktır.

Mikropsuz ortam olmayacağına göre intestinal floranın hangi bakterilerden oluşmasının tercih edileceği ve özellikle anne sütü ile bunun desteklenmesi önemsenmelidir.

## Özet

### Mikrobiyomlar ve Neonatoloji

**Amaç:** Mikrobiyomların Neonatoloji Döneminde kullanılması, fizyolojik floranın oluşturulması yanında, diğer etkileşimleri de gündeme getirmektedir. En belirgin belirtilen NEK oluşmasını önlediği eklindeki yayınlardır.

**Dayanaklar:** PubMed kaynaklı son literatürlerle konu irdelenmiştir.

**Giriş:** Neonatoloji Döneminde, özellikle prematürelere uygulamalarda, genel standart yaklaşım yerine belirli bir olgu temelli gruplandırma yapılması ve buna göre, beslenme değil, gastro-intestinal pasajın açık kalması ile fizyolojik floranın oluşturulması gündeme gelmelidir.

**Yaklaşım:** Çalışmaların Yöntemi belirli standart üzerine ve beslenme ile yapıldığı için genellikle NEK koruduğu ifade edilmiş olsa da fizyolojik floranın oluşması ile patolojik flora karşılaştırılmasının olmadığı anlaşılmaktadır.

Bebeklerin dışkılama, sindirme ve patojen ile oluşan flora farkı gözetilmelidir. NEK komplike konu olup, bunun tek mortalite nedeni gibi bakılması tam etki ve tepki gibi, kanıt dayanakları zayıf bir boyut oluşturmaktadır.

**Elde Edilenler/Sonuç:** İstatistiksel veri analizi yapılmış olsa bile, olay bireysel boyut ile ele alınmadığı için, olası zararlı olma boyutu da akla gelmektedir.

**Yorum:** Neonatoloji döneminde sağlıklı flora oluşması önemli yaşamsal boyut olduğu kanıta dayalı tıp kavramında olsa bile, pasaj açık kalması, ORS ve flora oluşması açısından sadece ağızdan verilmesi ile yeterli olamayacağı dikkate alınmalıdır.

**Anahtar Kelimeler:** Neonatoloji, Mikrobiyomlar ve NEK (Nekrotizan Enterokolit)

## Outline

### Microbiomes in Neonatology

**Aim:** The microbiomes on the Neonatology Perspective and the findings of the Researches are evaluated under the basic reality confrontation

**Groundings:** The PubMed and other literatures are discussed

**Introduction:** The validation of the findings is very important, whether to decide to give or not give any positive or negative conclusion at the Neonatology Period, thus, the establishing of the first intestinal flora is prime important. Primum non nocere is the Fundemantal of ethics principles, so, physiological flora confrontation cannot be substitute with pathogenic flora. The point is the benefit degree and evaluation of the utility concern.

**Proceeding:** The Standard procedures at the preterm cannot be as statistical basic application. The case cumulations and the acceptable concept must be figure out. The passage opening and the oral hydration and oral fluid feeding, not milk and other concepts are being discussed. Milk is not a good parameter whether to feed or not.

**Results:** The microbiomes research on the Neonatology is important evidences, thus, they are considering as the physiological flora establishing.

**Conclusion:** The basic starting of the researches are not acceptable, whether protective from NEC or not is not the aspect. The physiological flora and Pathological flora discrimination and the findings and the results must be evaluated, not the mortality and morbidity.

**Key Words:** Neonatology, Microbiomes and NEC (Necrotising Entero-colitis)

## Giriş/Introduction

Temel olarak mikrobiyaya bir tedavi olarak ele alınmamalıdır. Doğal ve fizyolojik basak, vücudumuzdaki floranın korunma ve gözetilmesidir. Bu doğal yapının yenidoğan döneminde oluşturulmasıdır. Bir doğal ile patolojik floranın tercihi boyutuna getirilmemelidir. Patolojik barsak florasına bağlı hastalıklar en sık prematüre ölüm nedenleri içinde iken, bunun Mikrobiyomların oluşması ile bir farklı boyut oluşmaktadır.

Başlıca: a) dirençli bakteriler oldukları için antibiyotiklere direnmektedirler, b) bu dirençleri patojen bakterileri geçirme olasılığı, üreme ortamları farklı olduğu için temas olanağı olmayacaktır, c) dokuya nekroz, apse ve tahribat yapmadıkları ve kanda üremeleri neredeyse imkânsız olacağı için, anaerobik olmaları ve pH açısından tercih edilen flora olmalıdır.

Literatür taraması ile Neonatoloji Dönemindeki yayınlara bakış atılacaktır. İngilizce sunum ile Türkçe yorumlar birlikte iletilmektedir.

NOTE: Microbiomes are physiologic intestinal flora, so the aim is to serve, protect and be on the natural, the physiological micro-organisms. Thus, in this Chapter the reports are discussed below, in Turkish and English evaluations of the presentations.

## About Literature indicated the using of microbiomes in Neonatal Period

Some articles concerning the using of probiotics at the newborn period are taken not as outline but by brief detailed one, for evaluating in comprehensively.

### 1) The using of Prebiotics at Neonatal Period/YENİDOĞAN BEBEKLERDE PROBİYOTİK KULLANIMI (2015) <http://drmetehanozen.com/yenidogan-bebeklerde-probiyotik-kullanimi/>

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NB: This article is in Turkish, but adapted to English in outline, not direct translation by M. A. Akşit MD.

#### Introduction

The meaning of the word “*probiotics*” in Greek Language as “*for life*”, thus, to be healthy for a long life. Thus, Metchnikoff used them for gastrointestinal problems and in Bulgaria mentioned as the reasoning for elongated lifetime. Meaning a beneficial effect on host. Leading to use widely in Neonatal Period, for nosocomial infections, feeding intolerance, necrotizing intolerance, and even sepsis in neonatology.<sup>1-8</sup>

### The developing of micro-flora in Newborns

Newborns are nearly sterile at the birth, but taken the microbes by mother's vaginal, fecal and body flora. Mainly effected by caesarian section, drugs taken by the mother, the stress factors, especially breast feeding or not. If the infant taken anti-infectives, *Bifidobacterium* spp. and *Bacteroides* spp., are remarkably reduced.<sup>9</sup>

Thus, the first cultured micro-organisms at the stool of the newborn are mainly facultative aerobic ones, then, they used oxygen and anaerobic bacteria are going to cultured.<sup>10</sup>

After birth, the colonic samples, at 48 hours, *Enterobacteria* spp., *Staphylococci* spp., *Streptococcus* spp., are the cultured ones. *Bifidobacterium* spp can be noticeable after 2-5 days of feeding with mother's milk. After the first week, *Bifidobacterium* spp are the dominant flora.<sup>11</sup> Bottle feeding newborn infants have 1/10<sup>th</sup> less *Bifidobacterium* spp. The protective mechanism at the mother's milk is effective.

Westerbeek at all<sup>12</sup> at the meta-analysis, at the six different researches, as advantageable microbes for the baby; *Bifidobacteria* spp., *Lactobacillus* spp., probable pathogenic ones; *Enterobacteria* spp., *E. coli*, *Bacteroides* spp., *Enterococcus* spp., *Streptococcus* spp., in addition of pathogenic micro-organisms; *Clostridia* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Klebsiella* spp, microorganisms are cultured.

Increasing of the *Bifidobacteria* spp, is important for developing of the gastro-intestinal immune system.<sup>13</sup> Enterobacteria is mostly established one at the bottle-fed infants.<sup>14</sup>

Probiotics added infant food is increased at the market,<sup>15</sup> and *Bifidobacteria* spp can be recordable at their stool cultures.<sup>16</sup>

At the Neonatology, Intensive Care Units, the cultures dominantly, the ward/service/unit micro-flora, thus the developing usual normal flora might be recordable at the third week.<sup>7</sup>

Therefore, supplementation of microbiota is essential for increasing the *Bifidobacteria* spp. Critical enhancement time is between the 30-35 Gestational Week, Median: 32.9 G. Weeks. The flora development can be encountered after third week of the labor.<sup>17</sup>

Breast feeding colonization, e.g. *Bifidobacterium*, is ten times more than bottle feeding. Mother's milk/secreting saliva-milk, has bioactive protective substances. The contribution to immune defense system is encountered by these microorganisms.<sup>11, 18-19</sup>

### Some known effects of Probiotics

There is a balance in the nature, as mentioned good and evil. In case of enteritis, even using anti-infective in infections, are mostly mentioned disturbing the natural flora.

- 1) At least a competition, the *Bifidobacterium* produces lactic acid and reduced pH, but others anaerobic and petrification, pH is increased, the basic environment conditions are differing.
- 2) The phosphorylation at "tight junction" is increased by actinide etc., the protective function of mucosa<sup>13</sup>.
- 3) Try to be at the epithelial contact.
- 4) Using the foods.
- 5) Bacteriocin. The mucus production is amplified, lymphoid tissue is activated, the superficial epithelial cell growth and differentiation is improved,
- 6) Anti-microbial peptides are depressed the growth of pathogens. Fecal IgA is noticeable after given *B. lactis*<sup>20</sup>.

**Table 1:** Some operative mechanisms of probiotics<sup>22</sup>

<b>Growth of the intestinal flora, other than the probiotics</b>	
	Reduced the pH of the intestine
	Secrete bactericidal substances
	Evoked to produce defensive at the epithelial and Paneth's cells
	Resist the colonization (by covering the ecologic niches)
	Increased the production of nitric oxide
<b>Barrier to attack and hang on the epithelia</b>	
	By stimulation of MUC2
	Increase the mucus production
	By depending to Rho or independently ways block the invasion of the epithelia
<b>Strengthened the epithelia and mucosal barriers</b>	
	The short chain lipid production like butyrate acid
	Increase the mucus production
	Increase the solidity of the barrier makes aspects
<b>Strengthen immune response of the host t</b>	
	IL-10, TGF beta, Cox2 (PGE2) expression and secretion
	IgA secretion immunoglobulin increased
	TNF and IFN-gamma expression is reduced
	Regulator T cells activated
	NK: Natural killer cells activated
	Dendritic cell phenotypes and regulation balanced
	NF-kappaB and AP-1 metabolic ways regulated
	PPAR-gamma stimulated
	Regulating the apoptosis
<b>Genetic Engineering</b>	
	IL-10 expression and secretion
<b>MUC2: mucine 2</b> <b>Rho: Guanosine triphosphate</b> <b>IL-10: Interleukin 10/suppressor</b> <b>TGF: Beta transforming factor beta</b> <b>Cox2: cyclooxygenase 2</b> <b>PGE: Prostaglandin E</b>	<b>TNF: Tumor necrosis Factor,</b> <b>IFN-gamma: İnterferon gamma</b> <b>NF-Kappa beta: Nuclear factor kappa B</b> <b>AP-1: Activator protein 1</b> <b>PPAR-gamma: Peroximal proliferating active recep1eu</b> <b>IgA: Immunoglobulin A, secretor</b>

This micro-flora has less endotoxins than Bifidobacterium's, thus at the infection state and at the mediator release stages, TNF alfa less activated. These leads, the TNF-alfa stimulation to p38/mitogen activated protein kinase, suppressed and cytokines induction to apoptosis is inhibited.<sup>21</sup>

These actions of the probiotics, at the maturation of intestinal mucosa and inflammation reaction of them is reduced and accepted as immune response not defense.

Probiotics has also extra actions on the undigested foods, facilitated the breakdown, synthesized new substances; as Vitamin K, Folic Acid, Biotin, B<sub>1</sub>, B<sub>2</sub>, B<sub>12</sub>, Pyridoxine and other vitamins.<sup>22</sup>

Lactase enzymes digest the milk sugar lactose. Lipids for the short chain structure reduced the pH of the intestine, this short chain lipids are also the energy product of the mucose,<sup>23</sup>

#### The Specifications and the Availability of Probiotics

Primary functional specificities are; a-non-pathogenic and nontoxic, b-human origin, c-resistant to gastric secretion pH, also to biliary acids, d-can survive and be in intestinal wall, e-suitable and friendly with natural flora, can be colonized, f-secrete antimicrobial substances, and g-positive contribution to host health.<sup>24, 25, 26</sup>

Common used ones; *L. rhamnosus* gg (lgg), *L. acidophilus*, *L. brevis*, *L. bulgaricus*, *L. reuteri*, *L. plantarum*, *L. salivarius*, *L. casei*, *Bifidobacterium bifidum*, *B. lactis*, *B. longum* ve *B. infantis*.

In market, there are some other species, *Escherichia*, *Enterococcus*, *Clostridium*, *Streptococcus* ve *Saccharomyces*.<sup>27,28</sup> Most common one is, *Lactobacillus rhamnosus*, thus mentioned as gg because of the first recorded researchers, S. Gorbach ve B. Goldin.<sup>29</sup>

In Pediatric age group, except *Lactobacillus rhamnosus*, the species used are; *Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Saccharomyces boulardii*, *Streptococcus thermophilus*, *Bifidobacterium animalis* and *Bifidobacterium bifidum*.<sup>30</sup> The best hanging, stuck and be at the mucosa is *Bifidobacterium animalis* spp. *Lactis*.<sup>31</sup>

Medically using and researches on using the probiotics in preterm, in Newborn Period is not satisfactory as mentioned from ESPGEN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition).<sup>32</sup> Thus more than 15 years, *Bifidobacterium* spp. put in the baby nutrition, not even any side effects at the doses 10<sup>8-10</sup> microorganisms at the supplements.<sup>33</sup>

#### The mode of consuming probiotics

There are some indicated for grounding to use at these conditions;

- Acute gastro-enteritis
- NEC=Necrotizing Entero-Colitis
- Diarrhea associated to anti-infective
- Inflammatory bowel syndrome
- Great surgery performed patients
- Voyage diarrhea
- Lactose intolerance
- *H. pylori* infection
- Acute pancreatitis
- Urogenital system health
- Immunity stimulation
- Preventing of allergies
- Colorectal carcinoma
- Bladder carcinoma
- Serum cholesterol level reducing
- Hypertension

At the newborn period, a) prevention of acute gastroenteritis, b) strengthened the immune response and c) prevention of necrotizing enterocolitis.

#### In Acute Gastroenteritis

The duration and the symptoms of diarrhea is significantly reduced at the studies; open area, clinical and by researchers.<sup>35-40</sup> This is in some findings by *Lactobacillus rhamnosus* gg using in Peru.<sup>41</sup> Some other researchers used *B. bifidum* ve *S. thermophilus*, thus 24% decrease of the enteritis.<sup>42</sup>

At the ROTA virus enteritis, *L. Rhamnosus* gg (lgg), *Lactobacillus reuteri*, *Lactobacillus casei* and *Bifidobacterium animalis* spp *lactis* are approved the positive effect.<sup>43</sup> In a report<sup>44</sup> by giving *L. Rhamnosus* the decreased ratio; at concomitant diarrhea from 33.3% to 6.7 percent, the reduction at the ROTA virus born enteritis from 16.7% to 2.2%. The duration of enteritis is reduced with Oral Rehydration Fluid and *Lactobacillus rhamnosus* up to 2,4-3 days, indicated in Survey study.<sup>45</sup>

Some actions of the probiotics are; a-not wedged the pathogens to the epithelium, increased the immune defense, regulating the motility, suppressed the secretary mechanisms, increased forming mucine are the indicated ones.

#### In Necrotizing Enterocolitis

The oxygenation, the blood flow of gastrointestinal system, the physiological construction mainly not satisfactory developed at the preterm below or less than 1500-gram Gestational Weight. Estimation of perceptible as clinically, in preterm is 10-25%, and the causing to death is 20-30%. The main prevention is breast feeding, mother milk is the principle protection and vaginal delivery. Cesarean delivery and a long duration of anti-infective, pathogen micro-organisms colonization, the side and adverse effect of immune reactions to these colonization, cause ischemia, necrosis and later perforation occurred, thus, the flow of this microbes also leading to death, easily cultured at these anaerobic conditions, unlike microbiota.<sup>46</sup>

Some medical applications, mainly for breast feeding or if not possible in preterm, obligatory mother's milk given procedures lessened the NEC ratio.<sup>47</sup>

The Low Birth Weight infants, the intestinal flora mainly encountered as; *Enterococcus faecalis*, *Escherichia coli*, *Staphylococcus haemolyticus*. The cultures at NEC noticed newborn infants, the 40% isolated flora is *Clostridium perfringes*. *Lactobacillus* species are reduced; thus, this finding is one of the grounding of developing NEC. In some researches<sup>48-54</sup> by giving mother's milk and addition of microbiomes; *L. acidophilus* and *B. infantis*, even putting in the infant nutrition, the ratio of enterocolitis is decreased as 63%. Deshpande et al<sup>21</sup> at meta-analysis, if the microbiomes is given at the first 10 days, eve the NEC at the second stages, the ratio is statistically reduced.

Lin et al<sup>47</sup> at the 437 preterm infants, by randomised controlled study, by giving *L. acidophilus* and *B. Bifidum*, bid for 6 weeks; NEC incidence is reduced, also less death and sepsis neonatorum encountered, even no side effects have been encountered. Sepsis neonatorum is cultured proved ones.

Indrio et al<sup>5</sup> by adding probiotics, the emptying of the stomach is increased at the preterm. Deshpande et al<sup>55</sup> even very low birth weight infants, below 1500 grams at labor, is required administrated the probiotics at the first 10 days, at 2010, the incidence of NEC

lowered 30%, thus, death ratio is lowered, sepsis neonatorum is not changed, by indicating not any new researches needed for the lowering the NEC ratio, it's obvious finding.

Szajewska at al<sup>56</sup> confirmed the probiotics not changed the death ratio at sepsis and NEC, but lowered all the causes of death.

Alfaleh at al<sup>32</sup> at the meta-analysis, in 2010, analyzing at the 9 randomised control studies, probiotics reduced the mortality at the stages II and even at stages III, Nosocomial infections and TPN (Total Parenteral Nutrition) administration date period is unchanged. But no encountered any systemic infection due to the probiotics.

#### In Nosocomial Infections

The hospital intensive care duration of the preterm babies is so long, therefore, nosocomial infections encountered commonly, thus more often the reasoning of mortality and morbidity. The flora is mostly the intensive care unit micro-organisms, because of using antibiotics, delaying of mother's milk, requiring ventilation, repeating invasive procedures and other medical reasoning are the cause of it.<sup>57</sup> Several reports on the nosocomial infection studies, but mainly accepted morbidity lessening at the preterm.<sup>47-56</sup>

#### In Sepsis Neonatorum

At the long duration seen sepsis cases, *Candida* spp is the most common cultured one. Manzoni at al<sup>58</sup> given *L. Rhamnosus* to the very low birth weight infants, *Candida* colonization is significantly reduced.

Although several studies performed by randomised controlled, indicated that, sepsis neonatorum incidence is significantly reduced, thus, meta-analysis is not satisfactory yet.<sup>6</sup>

#### In Weight Gaining

Expected weight loss at preterm babies is between 10-15 percent of their body weight. The gaining of weights indicated in a research (Mohan at al<sup>20</sup>), by given *Bifidobacterium lactis* the improvement is 4 times higher at the probiotics given group.

#### In Feeding Intolerance

The digestion and metabolizing of the food, at the newborn period, especially at preterm infants are not so easy, so many problems, including intolerance is obvious.

Deshpande at al<sup>7</sup> research, very low birth weight preterm infants that administrated probiotics, complete nutritional state is shortened then bottle fed.

Rouge at al<sup>59</sup> indicated that (*Bifidobacterium longum* and *Lactobacillus rhamnosus*) have no effect to be at complete nutritional state, but when over 1000 grams the recordable benefit is noticeable.

#### In Infantile Colitis

The infantile colitis is one of the most administration reason for mothers to the physicians. At the 6<sup>th</sup> months of age. The symptom for essential of diagnosis is; healthy infant, feeding indicated as well, periodically restlessness, crying, spastic and bending the legs, flushing at the face, nearly at the duration of 3 hours in a day, nearly 3 times in a week, as for 3 weeks' duration. Colic meanly starting from at the second week of life, ending at 4-6



months. The exact path-physiological explanation is not made yet, but some evaluations are mentioned.<sup>60</sup>

Savino et al<sup>61</sup> at the randomised control studies, 45 infants (*Lactobacillus reuteri*) given and 45 simethicone administrated infants, follow-up results are; 95% decrease at probiotics group, 7% reduction at the simethicone group.

In other research<sup>62</sup>, 25 at 46 infants *L. reuteri* given, 21 at 46 placebos given, the average of crying duration and the severity of the crying and the attacks of the colic is remarkably reduced.

### Conclusion

The establishing verdicts especially on clinical findings by using microbiomes, are in increased inclination. Especially at the last decade, results on newborns and pediatric cases, indicating on some aspects as meta-analysis, the benefit of microbiomes. The using is therefore establishing. In future, more other products are going to use, in different perceptions.

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## Editor Contribution/Decision

### Eng

The probiotics is our natural habitat. The benefit is obvious, even at the Newborn period, especially for preterm infants, forming the natural flora, by the help of mother's milk.

The using of microbiomes are so old, more than thousands of years, that we know at the history, ancient; Babylon beer, North Mesopotamia people condensate barley fermentation, for Whisky, Mediterranean's wine, China sake, Asia kimiz as alcoholic, etc. Fermentation is still used, not only for making alcoholic drinks, mostly yoghurt as used.

Milk is the main food for infants; the supernatant of yoghurt for supplement of diarrhea in mineral water (ORF), mostly used one.

The microbiota can be essential for lactose intolerance, as using by yoghurt, diluted yogurt (ayran) and yogurt with some olive oil, vegetables (cacik) by also for milk fermentation, by kefir type forming alcohol and especially horse milk for using alcoholic drink.

In small communities, like island in oceans, the culture can be taken by the mouth flora, mostly proven person, and infant food must be half digested and mixed by mother's swallowing, same as the birds.

Sepsis is not only causing with micro-organisms, hypoxia or oxidative stress and intestinal distention or tissue trauma, crush cause same effects. The microbes mostly at these conditions, secondarily infected. Thus, sepsis indicates a complex condition, inflammation situation.

### TR:

Doğal floranın bulunması, özellikle ilk defa bir yapının gelişmesi ve prematürelde de bunun sağlanması ile doğal bir fizyoloji oluşturulmaktadır. Bu yapı binlerce yıldır insanlar ile doğa arasındaki bir dengenin varlığı, yaşamsal olarak devamlılık sağlamıştır. Yeni çevrenin bozulması, antibiyotikler ile yapılan değişim, sezaryen ile hastane Mikrobiyomların oluşması ile bu düzen bozulmakta ve yeniden doğaya dönüş aşaması başlamıştır.

Mikrobiyomların birçok faydası ötesinde, kana karışıp sepsis yapma olasılığı elbet olduğu iddia edilse bile, vücutta üremesi olanaksız görülmektedir. Buna karşın prematürelde intestinal sorunların oluşması, özellikle NEK gelişmesine mâni olduğu görülmektedir.

Kaynaklar konu ile ilgili makalelere ulaşılabilmesi açısından eklenmiştir.

## 2) [Variability in enteral feeding practices of preterm infants among hospitals in the SEN1500 Spanish neonatal network]

### PubMed

Moreno Algarra MC, Fernández Romero V, Sánchez Tamayo T, Espinosa Fernández MG, Salguero García E; Red SEN-1500  
An Pediatr (Barc). 2016 Nov 9.

### Introduction

Proper nutrition is one of the primary objectives in the management of preterm infants. However, lack of evidence on the best strategy to achieve this objective has led to a great variability in feeding practices. This variability may be related to the differences in the incidence of complications, such as necrotizing enterocolitis (NEC).

### Conclusion

There is great variability in enteral nutrition policies in VLBW in Spain. Although some differences are justified by the lack of evidence, there are other interventions that have proven to be effective, such as evidence-based protocols or access to donor milk. Implementation in all the units could reduce the incidence of NEC and improve the nutritional status

### Editor Contribution/Decision

#### Eng

This is a result of questioner, at Spanish Neonatal Network. It is a standardized approach to the preterm infants. Thus, individualized medical approach is required, but there will be a program for the preterm babies. Microbiota is importance of the feeding. For NEC, the most important microbiome is *Bifidobacterium longum*.

#### TR:

Prematüre Yoğun Bakımlarda uygulanan rehber yaklaşım temelinde, sorular ile elde edilen sonuçlar sunulmaktadır. Mikrobiyomların uygulandığı vurgulanmakta ve NEK açısından önemi belirtilmektedir. Mukozaya adezyon yapan mikrop olarak özellikle *Bifidobacterium longum* olması önemsenmelidir.

## 3) Impact of probiotics on necrotizing enterocolitis

### PubMed

#### Underwood MA.

Semin Perinatol. 2016 Nov 8.

A large number of randomized placebo-controlled clinical trials and cohort studies have demonstrated a decrease in the incidence of necrotizing enterocolitis with administration of probiotic microbes. These studies have prompted many neonatologists to adopt routine prophylactic administration of probiotics while others await more definitive studies and/or probiotic products with demonstrated purity and stable numbers of live organisms. Cross-contamination and inadequate sample size limit the value of further traditional placebo-controlled randomized controlled trials. Key areas for future research include mechanisms of protection, optimum probiotic species or strains (or combinations thereof) and duration of treatment, interactions between diet and the administered probiotic, and the influence of genetic polymorphisms in the mother and infant on probiotic response. Next generation probiotics

selected based on bacterial genetics rather than ease of production and large cluster-randomized clinical trials hold great promise for NEC prevention.

### Editor Contribution/Decision

Eng

The pathogenic intestinal flora, generally confirm tissue degenerations, even necrosis and other conditions, due to their culturing concepts. This, microbiomes usually even anaerobic media for cultivation, but by lactic acid formation, the pH lowering and not cause any damage to cell and cell metabolism. Thus, NEC is a result of questioner, at Spanish Neonatal Network. It is a standardized approach to the preterm infants. Thus, individualized medical approach is required, but there will be a program for the preterm babies. Microbiota is importance of the feeding perspective, means structure of the intestine will be safe for digestion. The adhesion function is mainly by Bifidobacterium; thus, they must be at flora.

TR:

Prematürelerde temel olarak Abdominal kompartıman sendromu oluşmaması ile birlikte, barsak kanlanması önemlidir. Gastro-intestinal yapının bozulmaması önemlidir ki emilim, sindirim sağlanabilsin. Patojen bakterilerin Gram negatif olmaları ile doku nekrozuna kadar giden tahribata neden oldukları da gözlemlendiği için, mikrobiyota bunların bağırsaktan bulunmamasına neden olduğu da dikkate alındığında, konu probiyotiklerin NEK önlediği olarak değil, fizyolojik yapının korunduğu ve gözetildiği sonucunda barsak yapısının düzgün ve fizyolojik işlevsel kaldığı söylenmesi daha anlamlı olacaktır. Özellikle mukozaya yapışan özellik Bifidobacterium olması temel alınmalıdır.

#### 4) [\[Probiotic associations in the prevention of necrotising enterocolitis and the reduction of late-onset sepsis and neonatal mortality in preterm infants under 1,500g: A systematic review\].](#)

PubMed

Baucells BJ, Mercadal Hally M, Álvarez Sánchez AT, Figueras Aloy J.

An Pediatr (Barc). 2016 Nov;85(5):247-255.

**Abstract:** Necrotising enterocolitis (NEC) is one of the most common and serious acquired bowel diseases a premature newborn can face. This meta-analysis was performed comparing different probiotic mixtures to ascertain their benefits as a routine tool for preventing necrotising enterocolitis and reducing late-onset sepsis and mortality in premature neonates of less than 1500g.

**Material and Methods:** A systematic review of randomised controlled trials, between January 1980 and March 2014, on MEDLINE, the Cochrane Central Register of Controlled Trials, together with EMBASE, was carried out. Studies with infants <1500g or <34 weeks were selected, discarding those with Jadad scores lower than 4.

**Results:** 9 studies were selected for further investigation, pooling a total of 3521 newborns. Probiotics were found to reduce the NEC incidence (RR 0.39; 95%CI: 0.26-0.57) and mortality (RR 0.70; 95%CI: 0.52-0.93), with no difference to placebo regarding late-onset sepsis (RR 0.91; 95%CI: 0.78-1.06). Finally, when analysing the different strands, the use of a 2-probiotic combination

(Lactobacillus acidophilus with Bifidobacterium bifidum) proved to be statistically significant in reducing all-cause mortality when compared to other probiotic combinations (RR 0.32; 95%CI: 0.15-0.66, NNT 20; 95%CI: 12-50).

**Conclusion:** Probiotics are a beneficial tool in the prevention of NEC and mortality in preterm neonates. Moreover, the combination of 2 probiotics (Lactobacillus acidophilus with Bifidobacterium bifidum) seems to produce the greatest benefits. However, due to the differences in probiotic components and administration, it would be wise to perform a randomised controlled trial comparing different probiotic mixtures.

### Editor Contribution/Decision

Eng

The microbiota that is selected are specifications of their mucosal attachment and other safe conditions. Therefore, the findings are a general expected confrontation. The physiology is the benefit for the living organisms.

TR:

Prematürelerin fizyolojisi tam oturmadığı dikkate alındığında, probiyotiklerin mukoza koruyucu ve aynı zamanda ortamı daha güçlü boyuta getirici olanların seçilmesi ile bu etkinin gözlenmesi bir doğal sonuç olarak bakılabilir. Fizyolojiyi desteklemek, korumak ve gözetmek yaşam boyutu ve süreci açısından önemli olduğu ve olacağı açısından bir uyarı olarak irdelenmektedir.

### 5) Prevention of necrotizing enterocolitis with probiotics: a systematic review and meta-analysis

PubMed

Sawh SC, Deshpande S, Jansen S, Reynaert CJ, Jones PM.

PeerJ. 2016 Oct 5;4: e2429.

**Abstract:** Necrotizing enterocolitis (NEC) is the most frequent gastrointestinal emergency in neonates. The microbiome of the preterm gut may regulate the integrity of the intestinal mucosa. Probiotics may positively contribute to mucosal integrity, potentially reducing the risk of NEC in neonates

**Data:** Structured searches were performed in: Medline, Embase, and the Cochrane Central Register of Controlled Trials (all via Ovid, from 2013 to January 2015). Clinical trial registries and electronically available conference materials were also searched. An updated search was conducted June 3, 2016. Randomized trials including infants less than 37 weeks gestational age or less than 2,500 g on probiotic vs. standard therapy. Thirteen additional trials ( $n = 5,033$ ) were found. The incidence of severe NEC (RR 0.53 95% CI [0.42-0.66]) and all-cause mortality (RR 0.79 95% CI [0.68-0.93]) were reduced. No difference was shown in culture-proven sepsis RR 0.88 95% CI [0.77-1.00].

### Editor Contribution/Decision

Eng

When there is blood positive culture is confirmed, they indicate that, there is no difference. This is an indication of preventing aspect. The microbiota acts especially inside of the intestine, not allow to cultivate the other microorganisms. If passed to blood, they cannot be effective, their grown media is as pH 5.5 and so on, producing

lactic acid, so not be any influences on the other bacteria in blood. So, the result is habitual for cultivation. The Bifidobacterium is mainly active for adhesion of mucosa; thus, they must be at the flora.

TR:

Koruma ve gözetmenin önemi ortadadır. Barsak içinde etkin olması beklenen probiyotiklerin, dokuda diğer patojenlere karşı etkisiz kaldığı ve klinik fark saptanmadığı da beklenen bir bulgudur, çünkü dokuda üremedikleri ve dolayısıyla etkileşim olmaması beklenmektedir. Florada özellikle *Bifidobacterium longum* olması beklenilmelidir.

## 6) A randomised controlled trial of the probiotic Bifidobacterium breve BBG-001 in preterm babies to prevent sepsis, necrotising enterocolitis and death: The Probiotics in Preterm infants (PiPS) trial.

PubMed

Costeloe K, Bowler U, Brocklehurst P, Hardy P, Heal P, Juszczak E, King A, Panton N, Stacey F, Whiley A, Wilks M, Millar MR.

Health Technol Assess. 2016 Aug;20(66):1-194.

**Study:** To test the use of the probiotic Bifidobacterium breve strain BBG-001 to prevent NEC, late-onset sepsis and death in preterm babies while monitoring probiotic colonisation of participants. Babies born between 23 and 30 weeks' gestation and randomised within 48 hours of birth. Exclusions included life-threatening or any gastrointestinal malformation detected within 48 hours of birth and no realistic chance of survival. Double-blind, randomised, placebo-controlled trial. Recruitment was carried out in 24 hospitals, and the randomisation programme used a minimisation algorithm. Parents, clinicians and outcome assessors were blinded to the allocation. Placebo: 1 ml of one-eighth-strength infant formula. Primary outcomes were an episode of bloodstream infection, with any organism other than a skin commensal, in any baby between 72 hours and 46 weeks' postmenstrual age; an episode of NEC Bell stage  $\geq 2$  in any baby; and death before discharge from hospital. Secondary outcomes included stool colonisation with B. breve.

**Result:** In total, 654 babies were allocated to receive probiotic and 661 to receive placebo over 37 months from July 2010. Five babies were withdrawn; 650 babies from the probiotic group and 660 from the placebo group were included in the primary analysis. Baseline characteristics were well balanced. There was no evidence of benefit for the primary outcomes {sepsis: 11.2% vs. 11.7% [adjusted relative risk (RR) 0.97, 95% confidence interval (CI) 0.73 to 1.29]; NEC Bell stage  $\geq 2$ : 9.4% vs. 10.0% [adjusted RR 0.93, 95% CI 0.68 to 1.27]; and death: 8.3% vs. 8.5% [adjusted RR 0.93, 95% CI 0.67 to 1.30]}. B. breve colonisation status was available for 1186 (94%) survivors at 2 weeks' postnatal age, of whom 724 (61%) were positive: 85% of the probiotic group and 37% of the placebo group. There were no differences for subgroup analyses by minimisation criteria and by stool colonisation with B. breve at 2 weeks. No harms associated with the interventions were reported.

**Conclusion:** This is the largest trial to date of a probiotic intervention. It shows no evidence of benefit and does not support routine use of probiotics for preterm infants. The increasing understanding of the pathogenesis of NEC and sepsis will inform the choice of probiotics for testing and better define the target population. Future Phase III trials should incorporate monitoring of the quality and viability of the intervention and colonisation rates of participants; cluster design should be considered.

## Editor Contribution/Decision

Eng

The evaluation parameters are not as mortality and morbidity. There are several factors concerning them. The probiotics main considerations are the physiological functioning of the intestine. The stool examination, as digestion, the flora establishing. Giving a probiotic have no meaning as the be a flora at the intestine.

TR:

Prematüre bebeklerin mortalite ve morbidite etkileyen çok faktörler vardır. Temel olarak probiyotiklerin işlevleri ile irdelenmelidir. Ağızdan verilmesi ile bunun bağırsak mukozasında yerleşmesi ve etkisinin sağlanması gerekir. Bunun anlaşılması dışkı analizi ve sindirim boyutu ile anlaşılabilir. Ayrıca tek Mikrobiyom yerine çoklu verilmesi ile karşılaştırılması anlamlı olabilecektir. Burada Bifidobacterium bir tipi kullanılmıştır. B. Breve Ülkemizde olmayan, yenidoğanda tam kullanılmayan, suşlardan biridir. Bu tür yerine daha etkin olan *Bifidobacterium longum* olup, bu tür yeni ve pek kullanılmayan olandır.

## 7) Probiotics in very preterm infants: The PiPS trial

PubMed

McKinlay CJ, Rebello C, Tarnow-Mordi W.

Lancet. 2016 Aug 13;388(10045):655.

Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial

**Abstract:** Probiotics may reduce necrotising enterocolitis and late-onset sepsis after preterm birth. However, there has been concern about the rigour and generalisability of some trials and there is no agreement about whether or not they should be used routinely. We aimed to test the effectiveness of the probiotic Bifidobacterium breve BBG-001 to reduce necrotising enterocolitis, late-onset sepsis, and death in preterm infants.

**Methods:** In this multicenter, randomised controlled phase 3 study (the PiPS trial), we recruited infants born between 23 and 30 weeks' gestational age within 48 h of birth from 24 hospitals in southeast England. Infants were randomly assigned (1:1) to probiotic or placebo via a minimisation algorithm randomisation programme. The probiotic intervention was B breve BBG-001 suspended in dilute elemental infant formula given enterally in a daily dose of 8·2 to 9·2 log<sub>10</sub> CFU; the placebo was dilute infant formula alone. Clinicians and families were masked to allocation. The primary outcomes were necrotising enterocolitis (Bell stage 2 or 3), blood culture positive sepsis more than 72 h after birth; and death before discharge from hospital. All primary analyses were by intention to treat. This trial is registered with ISRCTN, number 05511098 and EudraCT, number 2006-003445-17.

**Findings:** Between July 1, 2010, and July 31, 2013, 1315 infants were recruited; of whom 654 were allocated to probiotic and 661 to placebo. Five infants had consent withdrawn after randomisation, thus 650 were analysed in the probiotic group and 660 in the placebo group. Rates of the primary outcomes did not differ significantly between the probiotic and placebo groups. 61 infants (9%) in the probiotic group had necrotising enterocolitis compared with 66 (10%) in the placebo group (adjusted risk ratio 0·93 (95% CI 0·68-1·27); 73 (11%) infants in the probiotics group had sepsis compared with 77 (12%) in the placebo group (0·97 (0·73-1·29); and 54 (8%) deaths occurred before discharge home in the probiotic group compared with 56 (9%) in the placebo group (0·93 [0·67-1·30]). No probiotic-associated adverse events were reported.



**Conclusion:** There is no evidence of benefit for this intervention in this population; this result does not support the routine use of B breve BBG-001 for prevention of necrotising enterocolitis and late-onset sepsis in very preterm infants.

**Comment:** Not all probiotic strains prevent necrotising enterocolitis in premature infants. [Lancet. 2016]

### Editor Contribution/Decision

Eng

This spp of Bifidobacterium is not used commonly. As in indicated at the comment, not everyone is same effective as the others. This is a cumulative effective aspect thus; more than one probiotics will be used.

TR:

Prematürelerde fizyolojik floranın bağırsakta oluşturulması olduğuna göre, tekli değil, çoklu bir flora boyutu sağlanmalıdır. Ayrıca Saccorimices türü de olması tercih edilmelidir. Bakteri ve funguslar birlikte bir kümülatif sağlıklı flora oluşturulmalıdır. Etkin olanlar seçilmelidir.

### 8) [Reduction in necrotising enterocolitis after implementing an evidence-based enteral nutrition protocol in very low birth weight newborns]

PubMed

Sánchez-Tamayo T, Espinosa Fernández MG, Affumicato L, González López M, Fernández Romero V, Moreno Algarra MC, Salguero García E.

An Pediatr (Barc). 2016 Dec;85(6):291-299.

**Abstract:** An unexpected increase in the incidence of necrotising enterocolitis (NEC) cases was observed in our hospital. Just in case, our feeding policy could be responsible, it was decided to conduct a systematic review and develop a clinical guideline regarding enteral nutrition of very low birth weight infants (VLBW).

**Method:** A "before" (2011) and "after" (May 2012 - April 2013) study was performed on the new feeding protocol. This included initiation of enteral feeding in the absence of haemodynamic problems, a trophic feeding period of 5-7 days, and subsequent increments of 20-30ml/kg/day, of breast milk/donor human milk from the beginning. Probiotics were not administered.

PRIMARY OUTCOME: incidence of NEC II 2 Bell's stage. SECONDARY OUTCOMES: focal intestinal perforation, overall mortality and mortality due to NEC, nosocomial sepsis; weight at 28 days and 36 weeks; % of infants with weight <p10 at discharge; and length of stay.

**Results:** Of the 270 VLBW infants, 155 were included in the "before" group, and 115 in the "after" group. NEC significantly decreased (12/155 vs 1/115, P=.008). A decrease in mortality rate was also observed (17.4% vs 7.8%, P=.02). In four cases NEC was part of the sequence of events that led to death in the first cohort, with none in the second. There was no difference in the incidence of focal intestinal perforation or of the other secondary variables analysed.

**Conclusion:** Implementation of an evidence-based enteral feeding protocol leads to a decrease in incidence of NEC, without increasing hospital stay or the incidence of sepsis.

### Editor Contribution/Decision

Eng

This study is in positive factor, thus, not examined the functioning of the microbiota, just establishing the NEC and mortality concepts. Intestinal flora confrontations have several perspectives, this function is better to be confirmed than the NEC ratio.

TR:

Prematüre bebeklerin bağırsaklarındaki bu sorunlar nedeniyle, barsak işlevlerine bakılması, bunun yerine çoklu etkileşim olan NEK ve mortalite boyutu ele alınmasa daha doğal yapı ve fizyoloji ortaya konulabilecektir. Barsak işlevi ve mikrobiyota işlevlerinin irdelenmesi ile daha önemli katkı sağlanabileceği düşünülmektedir. Aynı zamanda kan kültür pozitifliği veya klinik tablo, distansiyonu ve sindirim gibi işlevlerin ortaya konulması daha bilime katkı sağlayabileceği düşünülmektedir. Her Mikrobiyom NEK konusunda etkin olmaması öngörülebilir.

## 9) Necrotizing enterocolitis and preterm infant gut bacteria

PubMed

Warner BB, Tarr PI.

Semin Fetal Neonatal Med. 2016 Dec;21(6):394-399.

**Abstract:** Necrotizing enterocolitis remains an intractable consequence of preterm birth. Gut microbial communities, especially bacterial communities, have long been suspected to play a role in the development of necrotizing enterocolitis. Direct-from-stool nucleic acid sequencing technology now offers insights into the make-up of these communities. Data are now converging on the roles of Gram-negative bacteria as causative agents, despite the dynamic nature of bacterial populations, the varying technologies and sampling strategies, and the overall small sample sizes in these case-control studies. Bacteria that confer protection from necrotizing enterocolitis have not been identified across studies. The beneficial effect of probiotics is not apparent in infants with birth weights <1000 g (these infants are at greatest risk of, and have the highest case fatality rate from, necrotizing enterocolitis). Further work should be directed to the modulating gut microbes, or the products they produce, to prevent this devastating complication of preterm birth.

### Editor Contribution/Decision

Eng

This considered that, the Gram-negative microorganisms are causing necrosis and other degenerative to intestine, and mucosa. Therefore, not to be obvious but, the physiological aspects may be examined.

TR:

Prematürelerin gebelik haftasına göre boyutlar değişmektedir. Bu açıdan 1000 gram altı bebeklerin yapısı farklıdır. Bağırsaklar steril olamayacağına göre, flora nasıl oluşturulmalıdır sorusu sorulmalıdır. Gram negatiflerin olmaması ve diğer patojenlerin oluşmaması arzu edilir. Bu probiyotikler olumlu olmasa bile, diğerlerinin patolojik yapısının oluşmaması da bir katkı sağlayabilecektir. Özellikle Bifidobacteriumların etkinliği olduğu vurgulanmaktadır.

**10)** The Probiotics in Pregnancy Study (PiP Study): rationale and design of a double-blind randomised controlled trial to improve maternal health during pregnancy and prevent infant eczema and allergy

PubMed

Barthow C, Wickens K, Stanley T, Mitchell EA, Maude R, Abels P, Purdie G, Murphy R, Stone P, Kang J, Hood F, Rowden J, Barnes P, Fitzharris P, Craig J, Slykerman RF, Crane J.

BMC Pregnancy Childbirth. 2016 Jun 3;16(1):133.

**Abstract:** Worldwide there is increasing interest in the manipulation of human gut microbiota by the use of probiotic supplements to modify or prevent a range of communicable and non-communicable diseases. Probiotic interventions administered during pregnancy and breastfeeding offer a unique opportunity to influence a range of important maternal and infant outcomes. The aim of the Probiotics in Pregnancy Study (PiP Study) is to assess if supplementation by the probiotic *Lactobacillus rhamnosus* HN001 administered to women from early pregnancy and while breastfeeding can reduce the rates of infant eczema and atopic sensitisation at 1 year, and maternal gestational diabetes mellitus, bacterial vaginosis and Group B Streptococcal vaginal colonisation before birth, and depression and anxiety postpartum.

**Methods:** The PiP Study is a two-centre, randomised, double-blind placebo-controlled trial in Wellington and Auckland, New Zealand. Four hundred pregnant women expecting infants at high risk of allergic disease will be enrolled in the study at 14-16 weeks gestation and randomised to receive either *Lactobacillus rhamnosus* HN001 ( $6 \times 10^9$ ) colony-forming units per day (cfu/day) or placebo until delivery and then continuing until 6 months post-partum, if breastfeeding. Primary infant outcomes are the development and severity of eczema and atopic sensitisation in the first year of life. Secondary outcomes are diagnosis of maternal gestational diabetes mellitus, presence of bacterial vaginosis and vaginal carriage of Group B Streptococcus (at 35-37 weeks gestation). Other outcome measures include maternal weight gain, maternal postpartum depression and anxiety, infant birth weight, preterm birth, and rate of caesarean sections. A range of samples including maternal and infant faecal samples, maternal blood samples, cord blood and infant cord tissue samples, breast milk, infant skin swabs and infant buccal swabs will be collected for the investigation of the mechanisms of probiotic action.

**Discussion:** The study will investigate if mother-only supplementation with *Lactobacillus rhamnosus* HN001 in pregnancy and while breastfeeding can reduce rates of eczema and atopic sensitisation in infants by 1 year, and reduce maternal rates of gestational diabetes mellitus, bacterial vaginosis, vaginal carriage of Group B Streptococcus before birth and maternal depression and anxiety postpartum.

### Editor Contribution/Decision

Eng

This C/S and vaginal delivery is obviously makes the differences at the intestinal flora.

TR:

Prematüreler ve tüm yenidoğanların vajinal doğması sağlanması hekimliğin bir görevi olmalıdır.

## 11) Microbial therapeutic interventions

PubMed

Grady NG, Petrof EO, Claud EC.

Semin Fetal Neonatal Med. 2016 Dec;21(6):418-423.

**Abstract** The microbiome comprises all the microbes living in and on the human body. Human cells are greatly outnumbered by bacterial cells; thus human health depends on the health of the microbial ecosystem. For the immature preterm infant, the microbiome also influences intestinal and immune system development. This has implications for short term morbidities such as neonatal necrotizing enterocolitis and sepsis, but also long term health outcomes. Optimization of the preterm infant microbiome is a growing topic of interest. The microbial world is not one of good versus evil, but rather one of community; thus optimization includes not only minimizing pathogens, but also enhancing beneficial organisms. Options for optimization include judicious antibiotic use, administration of supplements such as prebiotics or probiotics, and transfaunation procedures such as fecal microbial transplant or microbial ecosystem therapeutics. Potential for benefit as well as risk for each of these options will be discussed.

### Editor Contribution/Decision

Eng

This is a concept of fecal transplant, thus, for newborns the breast feeding is the optimum one.

TR:

Prematürelerin florasının oluşması açısından anne sütü ve emzirme ile alınan ve oluşan bağırsak florası en ideal boyuta geldiği anlamını taşımaktadır.

## 12) Use of probiotics and prebiotics in infant feeding.

PubMed

Bertelsen RJ, Jensen ET, Ringel-Kulka T.

Best Pract Res Clin Gastroenterol. 2016 Feb;30(1):39-48.

**Abstract:** Gut colonization by beneficial bacteria in early life is necessary for establishing the gut mucosal barrier, maturation of the immune system and preventing infections with enteric pathogens. Mode of delivery, prematurity, breastfeeding, and use of antibiotics are some of many factors that have been described to influence early life colonization. Dysbiosis, the absence of normal colonization, is associated with many disease conditions. Pre- and probiotics are commonly used as supplementation in infant formula, such as prebiotic oligosaccharides for stimulation of Bifidobacterium growth aiming to mimic the high levels of these commensal bacteria in the gut of breastfed infants. Studies suggest that probiotic supplementation may be beneficial in prevention and management of disease (e.g., reducing the risk of necrotizing enterocolitis in preterm infants and treatment of acute gastroenteritis in children). Although these studies show promising beneficial effects, the long-term risks or health benefits of pre- and probiotic supplementation are not clear.

### Editor Contribution/Decision

Eng

This one is a question and doubt on the new forthcoming.

TR:

Prematüre ve diğer Neonatoloji Döneminde, fizyolojinin sağlanması önemsenmelidir. Patoloji ile fizyolojinin karşılaştırılması bile yapılmamalı, fizyoloji devamlı desteklenmesi, doğal boyut getirilmesi önemsenmelidir.

### 13) Impact of oral probiotics on neurodevelopmental outcomes in preterm infants.

PubMed

Akar M, Eras Z, Oncel MY, Arayıcı S, Guzoglu N, Canpolat FE, Uras N, Oguz SS. J Matern Fetal Neonatal Med. 2017 Feb;30(4):411-415

**Abstract:** The aim of the study was to evaluate the neurodevelopment outcomes of very low birth weight (VLBW) preterm infants supplemented with oral probiotics for the prevention of necrotizing enterocolitis (NEC).

**Methods:** A prospective follow-up study was performed in a cohort of VLBW preterm infants enrolled in a single center randomized controlled clinical trial to evaluate the efficacy of oral probiotics for the prevention of NEC. Cognitive and neuromotor developments were assessed by using the Bayley scales of infant development II. Sensory and neurological performance was evaluated by standard techniques. The primary outcome was neurodevelopmental impairment at 18-24 months' corrected age.

**Results:** A total of 400 infants completed the trial protocol. Of the 370 infants eligible for follow-up, 249 infants (124 in the probiotics group and 125 in the control group) were evaluated. There was no significant difference in any of the neurodevelopmental and sensory outcomes between the two groups.

**Conclusion:** Oral probiotic given to VLBW infants to reduce the incidence and severity of NEC started with the first feed did not affect neuromotor, neurosensory and cognitive outcomes at 18-24 months' corrected age.

#### Editor Contribution/Decision

Eng

The mother's milk at the culture medium confirms an obvious differentiation at the cell lines. This finding at the probiotics may be not statistical important, but breast feeding is the right of the newborn infants

TR:

Prematürelerin insan olarak anne sütünü alması ve beslenmesi bir yaşam hakkı olarak görülmelidir. Gelişim aynı zamanda sosyal ve kültürel olarak ta anlamlıdır. Boşanma oranı prematürelerde sık iken, anne sütü ve Ülkemizde ise belirgin olarak aile yakınlaşmasını sağladığı görülmektedir.

### 14) Clinical Effects of Prebiotics in Pediatric Population

PubMed

Orel R, Reberšak LV.

Indian Pediatr. 2016 Dec 15;53(12):1083-1089.

**Abstract:** Prebiotics are non-digestible components of food that in a selective manner trigger the expansion of microbes in the gut with valuable effects for the health of the host. In our document,

current literature pertaining to the clinical effects of the use of prebiotics for the treatment and prevention of some common pediatric pathology such as infantile colic, constipation, absorption of minerals, weight gain, diarrhea, respiratory infections, and eczema is reviewed.

**Evidence:** Data was collected through search of the MEDLINE, PubMed, UpToDate, Cochrane Database of Systemic Reviews, and the Cochrane Controlled Trials Register database as well as through references from relevant articles, all until September 2015. However, only the results of publications with adequate methodological quality were included.

**Results:** Prebiotics seem to be very appealing in treatment of many clinical conditions, explicitly in the fight against constipation, poor weight gain in preterm infants, and eczema in atopic children. In contrast to probiotics, the evidence of true clinical efficacy of prebiotics, supported with exact type and dose information are rather sparse, and there are a limited number of randomized controlled trials concerning prebiotics in children, especially beyond the age of infancy.

**Conclusion:** Large well-designed, controlled, confirmatory clinical trials are required, using commercially available products, to help healthcare providers in making an appropriate decision concerning the appropriate use of prebiotics in different conditions.

### Editor Contribution/Decision

Eng

This is an action for establishing the physiological flora.

TR:

Prematüre değil tüm bireyler için temel sağlık yaklaşımı, doğal fizyolojik yapının oluşmasıdır. Bağırsak yapılanması da bunun içindedir.

### 15) Survey and evidence based review of probiotics used in very low birth weight preterm infants within the United States

PubMed

Viswanathan S, Lau C, Akbari H, Hoyen C, Walsh MC.

J Perinatol. 2017 Jan;37(1):104. doi: 10.1038/jp.2016.181.

**Methods:** A prospective follow-up study was performed in a cohort of VLBW preterm infants enrolled in a single center randomized controlled clinical trial to evaluate the efficacy of oral probiotics for the prevention of NEC. Cognitive and neuromotor developments were assessed by using the Bayley scales of infant development II. Sensory and neurological performance was evaluated by standard techniques. The primary outcome was neurodevelopmental impairment at 18-24 months' corrected age.

**Results:** A total of 400 infants completed the trial protocol. Of the 370 infants, eligible for follow-up, 249 infants (124 in the probiotics group and 125 in the control group) were evaluated. There was no significant difference in any of the neurodevelopmental and sensory outcomes between the two groups.

**Conclusion:** Oral probiotic given to VLBW infants to reduce the incidence and severity of NEC started with the first feed did not affect neuromotor, neurosensory and cognitive outcomes at 18-24 months' corrected age.

### Editor Contribution/Decision

Eng

This is positive or negative perspective consideration, thus, physiological intestinal flora establishing.

TR:

Burada temel olan fizyolojik yapının oluşturulmasıdır.

## 16) [Research progress of the application of probiotics in preterm infants].

PubMed

Gan X, Li J

Zhongguo Dang Dai Er Ke Za Zhi. 2016 Sep;18(9):909-914. Chinese

**Abstract:** The gastrointestinal structure, function and immunity of preterm infants are immature. Furthermore the gastrointestinal microbe colonization is abnormal. Therefore the preterm infants are prone to a variety of gastrointestinal diseases. Probiotics can regulate gastrointestinal microbe constitute, improve gastrointestinal barrier function, reduce gastrointestinal inflammation response and regulate the immunity. At present, it is used for the prevention of necrotizing enterocolitis, late-onset sepsis, and feeding intolerance. The safety and efficacy of probiotics for preterm infants are still controversial.

### Editor Contribution/Decision

Eng

The degeneration of functional physiological flora, later on, means because of several diseases, mostly source on the intestinal pathologic flora.

TR:

Prematüre yanında tüm insanlık boyutunda patolojik ve her zaman içimizde bir bomba gibi patlayacak bir boyut yerine sağlıklı ve fizyolojik floranın oluşması önemsenmelidir.

### Son Yorum/Comment

Bir işleve bakarak ondan fayda veya faydasız olduğu ancak yaptığı işe göre irdelenmelidir. Bağırsaktaki floranın işlevleri dikkate alınmalıdır. Sadece NEK oluşup oluşmaması değildir işlevi. Ağızdan verilmesi ile yeterli olması yerine, besine katılarak yoğurt olması ile verilmesi daha öncelikli boyut kazandıracaktır. Gıdanın sindirilmesi, bağırsağın işlevlerine bakılmalıdır. Tek Mikrobiyom yerine çoklu boyutun oluşması ve birbirini desteklemesi önemsenmelidir.

Temel amaç fizyolojinin sağlanması ve sonra takip, desteklenme ve korunmasıdır. Eğer NEK gözlenme boyutunda önemli sonuç alınmaz ise, fizyolojinin desteklenmesinden vaz mı geçilecektir?

Mukoza ile yapışan *Bifidobacterium longum* tanımlanmaktadır. Dolayısıyla NEK konusunda etkinlik ancak bu mikrop ve bu tarzda işlevi olan ile bakılması uygun nitelikte ölebilecektir.

# Oral Re-Hidrasyon Sıvısı /Oral rehydration therapy (ORT)

Gastro-intestinal sistem sorunlarında özellikle sütü hazmetmesi beklenilmemelidir. En zor sindirilebilecek gıdalardan biridir, süt. Bu açıdan bu konuda doğrudan metabolize edilip yararlı olması değil, bunun aşama olarak gelişmesi beklenilmelidir. Sindirim işlev aşamaları sadece besinler ile olmamaktadır.

Hidrasyon önemli boyuttur.

- Oral sıvı alınması, özellikle elektrolitli sıvı belirgin farklıdır.
- Ağızdan süt veya ayran alınması da sindirim açısından önemli farklılıklar göstermektedir.
- Cacık ile ayran belirgin farklıdır, içinde bitkisel esansiyel yağ ile salatalık gibi sebzeler de vardır.

Bazı ORS Solüsyonları aşağıdadır

**Tablo 1:** ORS Solüsyonları ve Kapsamları

Solüsyon	Carbohydrate (g/dL)	Sodium (mEq/L)	Potassium (mEq/L)	Base (mEq/L)	Osmolality
Pedialyte	2.5	45	20	30	250
Infalyte	3	50	25	30	200
Rehydralyte	2.5	75	20	30	310
WHO/UNICEF*	2	90	20	30	310

**Tablo 2.** Diğer kullanılan ORS yaklaşımları

Solution	Carbohydrate (g/dL)	Sodium (mEq/L)	Potassium (mEq/L)	Base (mEq/L)	Osmolality
Elma Suyu	12	0.4	26	0	700
Ginger ale	9	3.5	0.1	3.6	565
Sit	4.9	22	36	30	260
Tavuk Suyu	0	2	3	3	330

## Temel Yaklaşım Boyutları

- Pasajın açık kalması
- Sıvı ve elektrolitlerin alınması
- Yarı sindirilmiş ve sıvı besinlerin alınması
- Beslenme, bazal kaloringin ve temel gereksinimin sağlanması
- Büyüme ve gelişmeyi sağlaması
- Besinin metabolize edilmesi ve atıklardan uzaklaşma



### Pasajın açık kalması

Bir iki damla anne sütü, oral-anal refleksin oluşturulabilmesi veya emzik ile tükürük ve oral sekrete olanın alınması bile pasajı açık sağlayabilir. Pasaj açık olmaz ise, emilim değil, zamanla atoni ve bağırsakta ters geçiş, sekresyon birikmeye başlar.

Sindirim faaliyeti sırasında barsakta erişkin için 5-7 litre sıvı toplanabildiği ve bu sıvı ile besin dengesi sağlandıktan sonra emildiği dikkate alınmalıdır. Bu nedenle baklava veya ağır yemeklerde susamak doğal bir boyuttur. Yemekten sonra koşmamakta aynı şekilde kanın farklı alana kayması nedeniyle adalelerin ve beynin kanlanmasının yeterince olamamasıdır.

### Pasajın açık kalması için sıvı ve elektrolitler

Barsak işlevine göre sıvı ve elektrolitler verilmelidir. Çok hızlı emilmesi ötesinde intravenöz verilmesinin çok üstünde verilebilmesi ile özellikle saha çalışmalarında, kolera salgınlarında önemi belirgindir.

### ORS'nin Fizyolojiye göre en az 3 farklı yapıda olması beklenir.

#### Kolera tipi ishalde

- Burada yüksek tuz atımı olduğu için ilk çıkan WHO solüsyonlarında 120 mEq/L Na var iken, Hiper-natremi yaptığı gözlemlendiği için bu doz 90 mEq/L kadar indirilmiştir.
- Damardan verilecek sıvı şok tedavisinde olduğu gibi kan elektrolitlerine yakın Ringer de olduğu gibi 130 mEq/L veya SF (154 mEq/L) ve ayrıca ½ SF (75 mEq/L) verilmektedir. Bu sıvılarda şeker olmaması nedeniyle ketozisi önlemek için dekstroz katılması (%6g üstü-10g gibi) gerekir  
Kolloid onkotik basınç açısından da dextran kullanılabilir. Anestezi Starch kullanmakta ancak dextran uygulanması Neonatoloji pratiğinde seyrek olsa da vardır.
- Halen Önerilen Toz/Litre eritilecek olan.  
WHO-ORS (düşük osmolar ORS veya azaltılmış osmolar ORS tanımlanmaktadır):
  - 2,6 gram (0.092 oz) tuz (NaCl),
  - 2,9 gram (0.10 oz) [trisodium citrate](#) dihydrate,
  - 5 gram (0.053 oz) potassium chloride ([KCl](#)), ve
  - 13,5 gram (0.48 oz) [anhydrous glikoz vardır.](#)
- Ülkemizde bulunan GeOral [http://www.kansuk.com/.../ge\\_oral.htm](http://www.kansuk.com/.../ge_oral.htm)

#### 1 poşette

Sodyum klorür: 2.6 g  
Trisodyum sitrat: 2.9 g  
Potasyum klorür: 1.5 g  
Glikoz, anhidr: 13.5 g

#### Editor Contribution/Decision

Eng

The WHO solution is high in Na, so there is risk of hyper-natremia, thus, all others are reduced to 45-70 mEq/L.

TR:

Burada temel olan fizyolojik olayın yakalanmasıdır. Bu açıdan hastaya bakılması gerekir.

- 1) Eğer hasta yeterli alamıyorsa;
  - a. 3-5 mL ağızdan 5 dakika ara ile verilmesi ile başlanması gerekir. Amaç midede birikim olmasın diye Waldeyer yolu ile midenin uyarılmadan, pilor stenozu olmadan boşaltılmasıdır. Bir saat içinde 10x3-5 mL ile saatte 300 mL sıvı verilebileceği dikkate alınmalıdır. Mide bulantısı olması demek, fazla verildiğidir ve kusması mide peristaltizmin uyarıldığı olup, daha az verilebilir. Bu şekilde tükürük uyarımı ile bir endojen kaynak başlatılmıştır. Barsak epiteli sindirimi ve gastro-intestinal işlevin de etkileşimi ile sekretuar değer emilim olacağı dikkate alınmalıdır.
- 2) Yeterli alıyorsa, bu durumda susuzluk nedeni fazla içebilir ve kusma olabilir. 30 mL fazla verilmemeli, pasaj olduktan sonra vermelidir. Bu 10-15 dakikadan kısa süreli oluşacaktır.
- 3) Günlük gereksinime/çıkarıldığından 20 mL/Kg ek verilmeli ve her çıkış için ek 20 mL/Kg kapsama göre arttırılarak veya azaltılarak verilmelidir.
- 4) Dehidratasyon durumuna göre fazla verilebilir. Prematürelere damardan verilen sıvı ile 760 mL/Kg kadar verildiği olmuştur, ancak zamanımızda plazma, dekstran veya diğer kombine verilmesi ile bu doza ulaşmak gerekmemekte, 20 mL/Kg SF ve muadillerinin verilmesi ile daha etkin düzelmekte ve bu doza iv ve ORS birlikte çıkılmamaktadır.

### Enterit türü ishalde

Burada laktöz intoleransı geliştiği için süt sorunludur, ancak ayran hem sulu, hem elektrolitli ve hem de probiyotik ile yarı sindirilmiştir.

- Önerilen yaklaşımlar Pedialyte ve benzeridir ama Na kapsamı biraz düşük kalmaktadır. Tercimiz 60 mEq/L olması uygundur.
- Sindirim işlevi yerine gelene kadar süt verilmemelidir.
- Kaka durumuna göre ayran ve özel multi probiyotik ile yapılmış yoğurt, birlikte elektrolitli sıvı tercihimizdir.

### Neonatoloji döneminde uygulamalar

Bebeklerin gebelik haftası ve fizyolojisine göre özellikle Na kapsamı düşürülmelidir.

Basit olarak SF ele alınırsa;

- SF 154 mEq/L
- 1/2 75 mEq/L
- 1/3 50 mEq/L
- 1/4 35-40 mEq/L
- 1/8-1/10 15-20 mEq/L

Prematürelere 1/8-10 mEq/L uygun ise onda bir sulandırılması ile ORS etkin olabilmektedir.

### Protein ve Yağ desteği

Bu ORS solüsyonlarında protein desteği yoğurt suyu/Whey Proteini 0.5 gram/dL olarak şekilde eklenmektedir. Yağ ise 2 gram/dL gibi bir oranda ayçiçeği, zeytin yağı eklemesi ile kullanılmaktadır. Bunun karşılığı 100 mL içine 1 mL konulması ile yeterli olduğu görülmektedir.

### Probiyotik desteği

- ORS içine probiyotiklerin katılması yapılmakta ve bu gerekirse ağıza 1-2 damla ile yapılmaktadır.
- Ayrıca ağıza ilk pasaj için damlatılan anne sütü içine katılarak ta uygulanmaktadır.
- Besleme özel mamalar içinde damlatılan probiyotikler ile, sıvı şişe 30-60 dakika yoğurt yapma makinesinde tutularak hem ısıtılması ve hem de mayalanması sağlanmaktadır. Yoğurt elbette tam olmakta, sulu olmakta ve yarı sindirilmiş olarak beslenme oluşmaktadır. Tolere etmede bir sıkıntı genellikle yaşanmamakta, residü oranı da çok seyrek.

### Başlıca Önerilen ORS Solüsyonları

Hacettepe Üniversitesinde 1972 yılında Pedialyte formülünde içine sitrat katılması yanında şeker oranı 6-8 gram ve dekstroz olarak uygulanarak adı Pedilit denilerek klinik uygulama yapılmıştır.

Eskişehir 1977 yılında Eczacı Özden ve Akşit adlarının bütünleşmesi ile ÖZAK olarak Tip 1 (90 mEq/L Na), Tip 2 (60 mEq/L Na) ve Tip 3 ORS (30 mEq/L Na) olarak kullanılmıştır.

Halen GeOral çocuğun kliniğine göre sulandırılarak kullanılmaktadır. K ise idrar yapınca konulmaktadır, ayrı hazırlanıp eklenmektedir.

ORS temel olarak gastro-intestinal sistemin sıvı emilim boyutunun çok üstün olduğu ve tolere etmesinde sorunların bazı durumlar dışında olasıdır. Eğer sıvı veya emilim olmaz ise, o zaman sekretuar boyuta kısaca ölü boşluğu kayıp olacaktır.

**Tablo 3:** Önerilen ORS Solüsyonları ve Kapsamları

Solüsyon	Dekstroz (g/dL)	Sodyum (mEq/L)	Potasyum (mEq/L)	Base (mEq/L)
ÖzAk 1-kolera	2.5	90	20	30
ÖzAk 1-enterit	2.5	60	25	30
ÖzAk 1-yenidoğan	2.5	30	20	30

# Neonatolojide Mikrobiyom

## Neden Neonatoloji?

Doğumda teorik olarak steril ortamda olduğu sanılsa bile, intrauterin olarak flora ile tanıştığı ve kordondan geçen antikorlar ve immün yapı ile anne florası ile tanış içinde olduğu söylenebilir.

Vajinal yol ile, flora alarak doğması önerilmekte, sezaryende ise çevreden alınanların sorun yarattığı veya yaratacağı ortaya konulmuştur Bu açıdan ilk ağıza verilen kolostrum ile birlikte dost Mikrobiyomların verilmesi veya alması önemsenmektedir.

Anne memesine Mikrobiyom sürülmesi bile katkı sağlamaktadır. Ayrıca mama alması ile de mamaya katılması veya ayrıca verilmesi önemli bir kazanç olmaktadır. Sadece bebeğe değil, aile içi flora oluşması açısından tüm köfte, yemek ve birçok cilt temizliğinde de anne, baba ve çocuklar bu flora içinde olması ile bir yaşam ortamı desteği sağlanmaktadır.

Bebeklerin bezleri, ortamdaki halı ve evdeki çiçek, vazo dahil tüm yaklaşımlarda Mikrobiyom kontrolü gereklidir.

Steril ortam yaratalım, dezenfekte edelim yaklaşım ile sadece 20 dakika gibi bir süreç mikropsuz ortam sağlayabilirsiniz. Her bakteri 20 dakikada bir bölündüğüne göre, hava ile kontaminasyonu temelinde, devamlı bir bulaş olacağı için floranın temizlenmesi değil kontrolü önemlidir.

Flora kaynağının temeli bizler, evdeki olanlardır. Bu açıdan kendi floramızı belirli mikroplardan oluşturursak, bebeğimizi de ortamı da sağlıklı oluşmasına katkımız olacaktır.

Bu nedenle olay geniş çevresel boyutla irdelenmiş ve teknik, besin hazırlama ve ev temizliği konusunda bilgilendirme yapılmıştır.

Sucuk ve köftenin kültürümüzden alınarak etkisi ve Mikrobiyom olarak anlamı ilgi çekme ötesinde arzu ve iştah oluşturarak sevgi/sevme boyutuna çıkması açısından geniş ele alınmıştır.

**SONUÇ:** Ağızdan alınan sıvı veya besinlerin ön sindirilmesi ve hazır olarak alınması, besini farklı yenilebilir boyuta getirmesi açısından Mikrobiyom önemli bir etkidir. Bu açıdan her şekilde alınan sıvı ve gıdalarda olması öngörmekteyiz. Bebeklerde ve prematürelere flora oluşması ve floranın ilk aşamada sağlanmasında önemli katkıları olduğu ve bu sayede ilaç olarak sunulanların ilk planda tercih edilmesi ve verilmesi önerilmektedir.

- Önce temel yaklaşım boyutu doğal fizyolojik intestinal flora oluşturulması
- Primum non nocere yaklaşımı esasları içinde patojen değil fizyolojik tek değil komple floranın sağlanması, anne süt ile bu yapının desteklenmesi gereklidir.