



Original / *Pediatría*

New clinical practice guideline on enteral feeding in very low birth weight infants; second part

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Abstract

Introduction: The nutrition of very low birth weight (VLBW) infants is aimed at promoting a similar growth to that occurring in the uterus. However, in practice this is difficult to achieve and extrauterine growth restriction is frequent. The current tendency is to avoid this restriction by means of early parenteral and enteral nutrition. Nonetheless, uncertainty about many of the practices related with nutrition has resulted in a great variation in the way it is undertaken.

In 2009 and 2011 in our hospital there was an unexpected increase in necrotizing enterocolitis. To check to see whether our nutrition policy was involved, we undertook a systematic review and drew up clinical practice guidelines (CPG) about enteral feeding in VLBW infants. New considerations about the duration of the fortification and the use of probiotics have led to an update of these CPG.

Methods: A total of 21 clinical questions were designed dealing with the type of milk, starting age, mode of administration, rate and volume of the increments, fortification, use of probiotics and protocol. After conducting a systematic search of the available evidence, the information was contrasted and summarized in order to draw up the recommendations. The quality of the evidence and the strength of the recommendations were determined from the SIGN scale.

Comment: These CPG aim to help physicians in their decision making. The protocolized application of well-proven measurements reduces the variation in clinical practice and improves results.

(*Nutr Hosp.* 2014;30:329-337)

DOI:10.3305/nh.2014.30.2.7590

Key words: *Low birth weight infant. Prematurity. Necrotizing enterocolitis. Probiotics. Clinical Practice guidelines. Evidence-Based medicine. Nutrition.*

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Recibido: 9-V-2014.
Aceptado: 9-VI-2014.

NUEVA GUÍA DE PRÁCTICA CLÍNICA SOBRE NUTRICIÓN ENTERAL DEL RECIÉN NACIDO DE MUY BAJO PESO AL NACIMIENTO; SEGUNDA PARTE

Resumen

Introducción: La nutrición de recién nacidos con peso muy bajo peso al nacer (MBPN) busca fomentar un crecimiento similar al que tiene lugar en el útero. Sin embargo, en la práctica, esto resulta difícil de conseguir y es frecuente encontrar una restricción del crecimiento extrauterino. La tendencia actual es evitar esta restricción por medio de una nutrición temprana parenteral y enteral. No obstante, la falta de certeza sobre muchas de las prácticas relacionadas con la nutrición ha dado lugar a una gran variación en los métodos.

En 2009 y 2011 en nuestro hospital se dio un aumento inesperado de enterocolitis necrosante. Para comprobar la posible implicación de nuestra política de nutrición, pusimos en marcha una revisión sistemática y redactamos unas directrices para la práctica clínica (DPC) sobre la alimentación enteral en recién nacidos con MBPN. Las nuevas consideraciones sobre la duración de la fortificación y el uso de probióticos han dado lugar a una actualización de estas DPC.

Métodos: Se definió un total de 21 preguntas clínicas sobre el tipo de leche, edad de inicio, modo de administración, porcentaje y volumen de los incrementos, fortificación, uso de probióticos y protocolo. Tras realizar una investigación sistemática de la evidencia disponible, la información fue contrastada y resumida para redactar las recomendaciones. La calidad de la evidencia disponible y la fuerza de las recomendaciones quedaron determinadas conforme a la escala SIGN.

Comentario: Estas DPC pretenden ayudar a los médicos en su toma de decisiones. La aplicación protocolizada de mediciones bien probadas reduce la variación en la práctica clínica y mejora los resultados.

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Palabras clave: *Recién nacido con bajo peso al nacer. Premadurez. Enterocolitis necrosante. Probióticos. Directrices para la práctica clínica. Medicina basada en la evidencia. Nutrición.*

Introduction

Nutrition for very low birth weight (VLBW) infants aims at promoting growth, similar to what takes places in utero, but without putting undue stress on metabolic and excretory functions. In practice this is difficult to achieve. In many cases the outcome is extrauterine growth restriction which often exacerbates prior intrauterine growth restriction.¹ The current trend is to avoid, wherever possible, extrauterine growth restriction through early, aggressive parenteral nutrition (with nutrients similar to those the foetus would receive through the placenta) and enteral feeding as early as possible.

At our hospital, in 2010 and 2011, we saw an unexpected increase in the incidence of necrotizing enterocolitis (NEC). To check to see whether our nutrition policy was involved, we undertook a systematic review and drew up clinical practice guidelines (CPG) about enteral feeding in VLBW infants.

Methodology

Several health professionals were involved in preparing this document, and they practice at the

Neonatal Unit of the Hospital Regional Universitario de Málaga. In addition, the coordinator of the Carlos Haya Hospital Complex Integrated Training Unit took part as an expert in methodology, documentation, and development of literature-search protocols. Likewise people with strong experience in the field of nutrition took part as external reviewers.

To formulate the key questions, health professional crew, used the PICO format—patient, intervention, comparison, and outcomes. With regard to assigning level of evidence and degree of recommendation we used the Scottish Intercollegiate Guidelines Network (SIGN) scale (table I).

After search, evaluation and selection of available scientific evidence, the recommendations are drawn to answer the key questions. Methodology and search strategy are widely described in part one.

Results

A total of 21 clinical questions were formulated (table II). Those regarding the time of onset and type of milk were already discussed in the first part of the guide. In response to the rest, we have drafted the recommendations which are discussed below.

Table I

Levels of evidence and grades of recommendation according to the Scottish Intercollegiate Guidelines Network

Levels of evidence

1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials, or clinical trials with high risk of bias.
2++	High-quality systematic reviews of cohort or case-control studies Cohort or case-control studies with very low risk of bias and a high probability of establishing a causal relationship.
2+	Well-conducted cohort or case-control studies with a low risk of bias and a moderate probability of establishing a causal relationship.
2-	Cohort or case-control studies with a high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports, case series or descriptive studies.
4	Expert opinion.

Grades of recommendation

A	At least one meta-analysis, systematic review, or RCT, rated as 1++ and directly applicable to the guideline's target population; or a body of evidence composed of studies rated as 1+ and with overall consistency among them.
B	A body of evidence composed of studies rated as 2++, directly applicable to the guideline's target population and demonstrating overall consistency among them; or evidence extrapolated from studies rated as 1++ or 1+.
C	A body of evidence composed of studies rated as 2+ directly applicable to the guideline's target population and demonstrating overall consistency among them; or evidence extrapolated from studies rated as 2++.
D	Level of evidence of 3 or 4; or evidence extrapolated from studies rated as 2+.

Good clinical practice

√	Recommendation of good clinical practice based on the clinical experience of the group that developed the guideline.
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Table II

Twenty-one questions to be answered by the clinical practice guideline with regard to enteral feeding in infants less than or equal to 32 weeks gestational age and/or 1,500 g in birth weight

1. Should premature infants who have just born be nil by mouth or should trophic enteral feeding be started instead?
2. At what age after birth should feeding begin?
3. Are there particular situations where the start should be delayed?
 - 3.1. If breast milk is not available
 - 3.2. IUGR with no evidence of absent or reversed end-diastolic flow in the umbilical artery
 - 3.3. IUGR with absent or reversed end-diastolic flow in the umbilical artery
 - 3.4. Umbilical artery catheter
4. Which type of milk should be used to start feeding in premature infants who fulfil the above-cited characteristics?
5. Once feeding has been started, should trophic feeding be continued or should daily progressive increases be made?
6. What should the amounts and rate of increases in milk intake be?
7. What is the recommended method for administering feeding: bolus vs. continuous enteral?
8. Should we fortify breast milk?
9. In premature infants < 1,500 g, should fortification be continued after hospital discharge?
10. What would be the best approach to follow with regard to the use of fortifiers once the infant is breast-feeding directly?
11. Does standardizing the method of enteral feeding cause any benefit versus doing it based on a specific medical criterion?
12. Should the use of probiotics be recommended?
13. Should probiotics be used in all infants or only in those who are at risk and do not fulfil the exclusion criteria?
14. Should probiotics be used in infants who fulfil the criteria, regardless of whether they have been receiving antibiotics?
15. Should probiotics be used at all centres or only at those with a high rate of NEC?
16. How long should they be administered?
17. Administration of probiotics: Single strain versus multiple strains
18. What would be considered to be the most appropriate dose?
19. Should probiotics be administered only to infant formula or to any type of milk?
20. Prophylactic or therapeutic administration?
21. Can the administration of probiotics to premature infants be considered safe and effective?

Recommendations for clinical practice guideline

Should feeding be started with a trophic period or directly with gradual increases?

The beneficial role of TEF has been previously discussed. In animal studies, the lack of nutrients in the gastrointestinal tract as result of prolonged fasting, was associated with decreased intestinal growth, mucosal atrophy, delayed maturation of intestinal enzymes, changes in perfusion, decreased gastrointestinal permeability, and therefore, a higher risk of bacterial translocation. These same studies demonstrate how early enteral feeding leads to a two- to threefold increase in gastrointestinal mucosal mass. This trophic effect might be mediated by several growth factors, such as insulin, epidermal, and other peptides, all of which are found in human milk. We can conclude that early enteral feeding prevents gastrointestinal atrophy, appears to stimulate the maturation of the gastrointestinal system, and may improve feeding tolerance, especially when colostrum

and human milk are used. Hence the most appropriate strategy for starting successfully and afterwards increasing enteral feeding amounts would be to begin with “minimal or trophic enteral feeding.”

By contrast, rapidly increasing enteral feeding amounts might lead to an increase in NEC figures. Berseht conducted a trial comparing a group where TEF with breast milk or formula at 20 ml/kg/day for 10 days was administered, to a second group with daily increases of 20 ml/kg/day from the first day of feeding. This trial established criteria for stopping the study if differences in the rate of NEC were observed when performing intermediate evaluations. The study was stopped when 144 infants had been enrolled, after objectify a lower incidence of NEC in the group that continued with trophic enteral feeding (1/70 vs. 7/74). It should be noted that no statistical significance was reached with this number (RR = 0.14, 95% CI: 0.02; 1.07). The group that was fed with trophic amounts had to stay in the hospital longer, though there was no statistical significance.

One of the limitations of this study is that feeding was started very late, around 9 days, which does not seem to be the practice that is widely used these days.²

The multicentre case-control study by Henderson cited above, showed that making increases at a faster rate may act as a risk factor for developing NEC.^{2,3} (**evidence 2++**).

Summary of the evidence

1+ In VLBW infants < 32 weeks gestational age, who have undergone prolonged fasting, starting feeding with daily increases of 20 ml/kg increases the risk of NEC compared with giving trophic feeding without daily increases.

2++ The shortest duration of trophic feeding and a faster rate of increases are related to a higher rate of NEC.

Recommendations

B Increases in milk should be made after a trophic period that varies based on risk of NEC (usually from 5 to 7 days).

B In premature infants who have had a period of prolonged fasting, trophic feeding should be started, without increasing the amounts during the first days.

How should the amounts and rate of breast-milk intake be increased and by how much?

After progressive feeding has been started, the traditional rate of increasing it has been 20 ml/kg/day. Based on a recent meta-analysis comparing different amounts of increases after one week of TEF it may be increased by up to 30-35 ml/kg/day. We cannot generalize this recommendation to include infants who weigh less than 1,000 g, are extremely premature, have IUGR, or are on mechanical ventilation, because the meta-analysis included few patients with these characteristics. This study concluded that with these increases, full enteral feeding was reached early on and birth weight regained without increasing the risk of NEC, compared with smaller daily increases⁴ (**evidence 1+**).

Summary of the evidence

1+ Rapid increases (up to 30-35/ml/kg/day) achieve a reduction until full enteral feeding is reached and birth weight regained. There were no effects on NEC (relative risk = 0.90; CI 95%: 0.46; 1.77).

*The trials on which it is based are generally conducted with infants > 1,000 g, and so they cannot be extrapolated to extremely low birth weight infants.

*Increases were generally performed around the first week of life and after a trophic period, and so any

effect they might have if started in the first days is not known.

Recommendations

A After the “trophic feeding period”, daily increases of up to 30 ml/kg/day are to be made, while monitoring digestive tolerance.

C In infants < 1,000 g, there is no evidence of the safety of these amounts, and so the recommended increases are 10-20 ml/kg/day.

√ We propose increases of 10-15 ml/kg, which are to be increased on an individual basis twice daily, in order to monitor tolerance.

*10 ml/kg every 12 hours in infants < 1,000 g or with > digestive risk (up to 20 ml/kg/day). *With this, 100 ml of milk/kg/day is reached by day 4 of the increases.*

*15 ml/kg every 12 hours in infants > 1000 g (up to 30 ml/kg/day). *With this, 100 ml of milk/kg/day is reached by day 3 of the increases.*

How to administer milk: bolus vs. continuous enteral?

Because of their immaturity, premature infants require tube feeding with nasogastric or orogastric tubes, which allow feeding to be done continuously or intermittently by bolus. Both methods can theoretically have benefits and risks. After comparing them, a Cochrane meta-analysis concludes that no recommendation can be established in that regard. Significant differences were found only in days needed to reach full enteral feeding (earlier by bolus), without observing differences in somatic growth, NEC incidence or hospital stay⁵ (**evidence 1+**).

Summary of the evidence

1+ There is no evidence of the benefit of either manner of administering enteral feeding (bolus vs continuous).

Recommendations

A No recommendation can be made for either type of feeding (bolus vs continuous).

Should we fortify breast milk?

To answer this question we will focus on a Cochrane meta-analysis⁶ which showed improved physical growth and head circumference in the short term. However, it showed no improvement in bone mineral content, probably because some of the tests included

phosphate supplements in the non-intervention group, considering it “unethical” to discontinue doing so. Nor is it conclusive with regard to long-term benefit, perhaps because there are few studies that prolonged follow-up. It does not appear to increase the incidence of serious adverse effects (NEC or death), although flaws in the studies make it difficult to rely on this statement.

Fortification improves short-term growth with no proven adverse effects. Composition and appropriate dosage still need to be established.

Summary of the evidence

1+ Breast milk fortification promotes short-term growth and has no adverse effects.

Recommendations

A Breast milk should be fortified for premature infants < 1,500 g or under 32 weeks.

In premature infants < 1,500 g, should fortification be continued after hospital discharge?

We found no strong evidence in this regard. Fortifying breast milk after discharge, whether by maintaining a preterm formula with mixed feeding, or with a human milk fortifier, does not seem to improve growth at one year of age. One study shows increased weight and bone mineral content, but not bone density,^{7,8} also observing that those not fortified ingest larger amounts of breast milk.

In addition, excessive catch-up growth during the period close to or after discharge has been linked to cardiovascular disease, hypertension, obesity, or type 2 diabetes in adulthood.

Amounts of approximately 200 ml of unfortified breast milk may be sufficient for adequate growth after discharge (not in the initial period), thus reducing the risk of excessive catch-up growth.

Summary of the evidence

1-Fortification after discharge does not improve long-term growth versus administration of amounts of 200 ml/kg/day of breast milk.

Recommendations

D We cannot establish a systematic recommendation for fortification following hospital discharge.

✓ Try to have them ingest large amounts of unfortified breast milk, while monitoring the growth chart and

efficacy of intake. If these amounts are not good, maintain fortification with smaller amounts of milk.

What would be the best approach to follow with regard to the use of fortifiers once the infant is breast-feeding directly?

To reiterate the argument above, fortification should be maintained until close to term, hospital discharge, or in any case until the premature infant can ingest approximately 200 ml/kg/day of unfortified breast milk. To this end, breast milk may be obtained; fortify it in two or three doses, and for the rest, breast-feed. Preterm formula would be maintained with mixed breast-feeding instead of term formula. Once sucking is clearly effective and after verifying adequate growth, we would discontinue this practice so as not to hinder the breastfeeding process.

Does standardizing the method of enteral feeding result in any benefit versus doing it based on a specific medical criterion?

In a systematic review and meta-analysis of observational studies, a reduction of 87% in the risk of NEC was found after the implementation of a standardized enteral feeding protocol. The individual results of these studies are also consistent (**evidence 2++**)⁸.

At least two studies that included practices such as TEF and breast milk fortification yielded similar results (**evidence 2-**)^{9,10}.

Summary of the evidence

2++ Standardizing the enteral feeding regimen with the maximum evidence to date may lead to a decreased incidence of NEC.

Recommendations

B In neonatology departments, the enteral feeding regimen for premature infants < 1,500 g and/or < 32 weeks should be standardized based on the latest evidence.

Is the use of probiotics effective and safe?

NEC remains one of the leading causes of death, especially in VLBW infants. When given prophylactically, probiotics may prevent NEC from developing by colonizing the gut with beneficial organisms—which in turn would prevent pathogens from colonizing it and thereby improve the maturation and barrier function of the intestinal mucosa—and by modulating the immune system. Increasingly, studies are advocating their administration to VLBW infants.

A Cochrane review published in 2011 by Alfaleh¹⁰ performed a meta-analysis of 16 clinical trials that included 2,842 children. This study concludes that oral administration of probiotics significantly reduces the incidence of severe NEC (stage II or higher) (RR 0.35; CI: 0.24-0.52) and mortality (RR 0.40; CI: 0.27-0.60), but not hospital-acquired infections (RR 0.90; CI: 0.76-1.07). None of the trials included reported systemic infections caused by probiotics.

Summary of the evidence

1++ The use of prophylactic probiotics reduces the risk of NEC and neonatal death, but not the risk of late-onset hospital-acquired infections. Clinical trials are consistent in these respects. The analysis of the variability among them, which is low, and the low rate of adverse effects puts the level of evidence at 1++ with a high grade of recommendation.

1+ They are equally effective and safe in premature infants with a birth weight of less than 1,150 g.

Recommendations

A Administer prophylactic probiotics to premature infants < 32 weeks gestational age and/or with extremely low birth weight who do not fulfil the exclusion criteria.

Should they be used at all centres or only at those with a high rate of NEC?

Individual studies have suggested that the potential benefit of probiotics is greater at centres with high rates of NEC, considering high rates to be more than 10%. However, studies by Linn in 2005 and 2008 repeatedly showed a reduction in NEC in the “probiotics” group regardless of the rate (1.1% vs. 5.3% with $p = 0.03$ and 1.8% vs. 6.5%, with $p = 0.02$ respectively), with a number needed to treat (NNT) of 24 and 21^{11,12}.

Summary of the evidence

1+ The beneficial effect “reflected” as relative risk remains similar at centres with lower rates of NEC (RR 0.38 vs. 0.32) or mortality (RR 0.36 vs. 0.35), compared to centres with higher rates. Logically, the NNT will be higher if the prevalence of NEC or neonatal deaths is lower at a given centre.

Recommendations

A It is recommended to use probiotics at centres with a high rate of NEC and at those with a low rate.

Should they be used in all patients or only in those who do not fulfil the exclusion criteria?

One of the main concerns with regard to the use of probiotics in premature infants is the possibility of developing sepsis associated with them. Though the protective effects of probiotics on mucosal integrity are well known, it is not known whether there is the potential for this integrity to be disrupted.

In addition, in case of changes in the intestinal barrier both pathogens as probiotics may be translocated and enter systemic circulation, thus causing sepsis.

To date, only six cases of sepsis associated with probiotics have been published, all in patients undergoing abdominal surgery (short bowel syndrome secondary to intestinal atresia, gastroschisis, omphalo-coele, and NEC) or heart surgery^{1,14,15}. No cases of sepsis associated with the use of probiotics have been described in clinical trials that have evaluated their use in premature infants, which as a whole includes more than 1,200 patients.^{16,17} In addition, pharmacovigilance data in countries where the use of probiotics is widespread have shown no evidence of an increased number of sepsis cases associated with probiotics.

Summary of the evidence

3 Most studies on the use of probiotics have been conducted in patients in situations where it was appropriate to start enteral feeding. There have been reports of infections caused by probiotic species in critically ill or haemodynamically unstable patients or those undergoing intestinal tract surgery or with heart disease, that compromised mesenteric blood flow.

Recommendations

D Administration is not recommended in critically ill patients or those with changes in intestinal mucosal integrity.

When should probiotics be administered, regardless of the use of antibiotics or otherwise?

The gastrointestinal tract of a healthy breast-fed premature infant is not colonized by *Bifidobacterium* and *Lactobacillus* until approximately the tenth day of life. In premature infants fed with formula, this colonization is less diverse, with approximately 50% of *Bifidobacterium*.

In premature infants, this colonization is delayed and may also be dominated by bacteria such as species of *Enterobacteriaceae* and species of *Clostridium*.

Because it is important that commensal flora colonize the gastrointestinal tract early on in premature

infants, it seems logical that supplements should be started as soon as possible^{18,19,20} before pathogens have the opportunity to start colonizing. Based on this, most investigators start them once the premature infants are ready to start enteral feeding. Clinical and haemodynamic stability are desirable in order to ensure the integrity of intestinal function and a minimal risk of food intolerance or translocation.

There is a significant association between pathogen colonization and the use of antibiotics.¹⁸ In addition, the use of antibiotics also destroys the commensal flora, and so the beneficial effect of probiotics will also be diminished during antibiotic treatment.

On this point the studies diverge: Guthmann²¹ et al. administered probiotics to premature infants < 32 weeks with a birth weight of < 1,500 g (who did not fulfil the exclusion criteria, usually from the second day of life and if they tolerated at least 2 cc of enteral feeding) starting the first day after discontinuing antibiotic treatment, and each time they received a series of the same, continuing with this for up to 14 days. Linn^{12,13} by contrast administered probiotics from the start of feeding, continuing with them regardless of the use of antibiotics, and discontinuing them only in case of sepsis, haemodynamic instability, or risk situations involving intestinal mucosal integrity. In no case were adverse effects reported.

Summary of the evidence

We found no trials that specifically analyze the ideal time to start using probiotics. Most started them after enteral tolerance began.

We found no studies evaluating the efficacy of probiotics administration during antibiotic treatment. But they have definitely been used, and have shown no added risk.

Recommendations

✓ Probiotics may be used from the start, maintaining them continuously except in cases of sepsis, ileus, or critical situations that put the premature infant's life at risk.

✓ When using antibiotics, it will be necessary to administer probiotics after completing the antibiotic treatment.

How long should they be administered?

We found no trials comparing different durations of use for probiotics.

The elimination of probiotic microorganisms in the stool usually disappears within 2 to 3 weeks of completing administration.^{18,19} As such, it seems that they should be continued while there is still the risk of digestive intolerance, developing NEC, or death.²⁰

Summary of the evidence

3 With regard to the results published and given the inverse relationship between gestational age and possibility of developing NEC, and all-cause mortality, it seems advisable to continue with probiotic supplements until 34 to 36 weeks corrected age, when the risk of these unfavourable results is reduced.

Recommendations

D Administer probiotics daily until 35 weeks corrected age or discharge.

Administration: Single strain versus multiple strains

Not all species of probiotics have proven effective, since not all act the same way. As the medical literature shows, the beneficial effects of a probiotic may be highly specific to that strain and may not be generalizable even to other strains of the same species. Although many studies have been carried out using a single strain, many investigators support the use of multiple strains in order to create conditions as similar as possible to those of a healthy child.¹⁴

An evaluation of the literature shows better results when two or more species of probiotics were administered with a single strain. However, we found no trials that compare the administration of one strain versus multiple ones, but only case series extracted from trials comparing them *versus* placebo.

Guthmann²¹ in his meta-analysis evaluating the prophylactic administration of probiotics in premature infants to prevent NEC, stratified and compared the results of several clinical trials that used one or multiple strains. It includes 11 trials, 4 of which used a single strain; 4 multiple strains; and 3 a specific combination of *L. acidophilus* + *Bifidobacterium spp*, which is the combination with the highest number of premature infants included and results published (499 and 488 premature infants in each trial arm) with an RR of 0.29 (0.15-0.56).

Summary of the evidence

1+ Clinical trials using multiple strains of probiotics prophylactically to prevent the development of NEC in premature infants have shown better results.

Recommendations

C Using a combination of probiotics that have been tested as effective versus a single strain is preferred.

✓ Use only species that have been shown to be effective and cause no adverse effects.

Should probiotics be administered only to infant formula or to any type of milk?

The overall beneficial effect has been shown both in children fed exclusively with breast milk (RR 0.31; 0.14-0.67) as with mixed breastfeeding (RR 0.38; 0.22-0.66) or exclusively with formula (23/146 vs. 10/157).

Summary of the evidence

1+ Probiotics reduce NEC and mortality regardless of the type of milk used.

Recommendations

A Probiotics should be administered regardless of the type of milk used.

What would be considered the most appropriate dose?

It seems reasonable to think that there should be an optimal dose for the probiotic to be able to survive and overcome the barriers posed by gastric acid, bile, and commensal flora, thus proliferating and colonizing the gastrointestinal tract. At present the optimal dosage is not known. The results published show efficacy with minimum doses of 10^6 - 10^7 colony-forming units (CFU).²²

Most studies use doses of 3×10^9 CFU in infants 32 weeks gestational age, with efficacy and no adverse effects observed.

Summary of the evidence

2++ The mean dose used in clinical trials with premature infants < 32 weeks gestational age, and which has proven effective and safe, is 3×10^9 CFU.

Recommendations

D Experts recommend starting with half the dose, 1.5×10^9 , while the amount of milk is low (less than 50-60 ml/kg/day) because there may be problems of high osmolarity, and in addition, there are theoretical risks of poor intestinal transit.

C Increase to 3×10^9 when larger amounts are reached.

Prophylactic or therapeutic administration of probiotics?

The beneficial effect of probiotics has been shown when they are administered prophylactically.

Therapeutic use in cases of NEC or ileus has not been tested and entails theoretical risks. The risk of probiotic translocation and, as a result, of sepsis, is greater in critically ill VLBW patients who are at a potential risk for loss of intestinal integrity. There are no data justifying the use of probiotics in cases of suspected acute disease.^{23,24,25}

Summary of the evidence

There are no data on the use of probiotics for critically ill premature infants.

3 Data extrapolated from clinical trials in critically ill adults, comparing administration of a probiotic versus placebo, have shown increased mortality in the probiotic group.

Recommendations

D A therapeutic recommendation for the use of probiotics in confirmed NEC and suspected sepsis or serious acute disease cannot be made.

Final comments

“The idea that a single method will work for all children in all cases is unrealistic.” Although this quotation by Hany Aly, which refers to non-invasive ventilation, could be applied to enteral feeding of premature infants, it is also true that the application of standardized measures reduces variability in clinical practice and achieves better results.

We believe that in a stable VLBW infant with a good Apgar score and without vasoactive or aggressive respiratory support, early trophic feeding should be started (no more than 2nd-3rd day) with breast milk. Haemodynamically unstable infants should be made to continue fasting. After a trophic period (longer in infants at higher risk), proceed with daily increases of up to 30 ml/kg/day in older infants weighing 1,000 g, and more cautious increases in younger infants or those with risk factors for NEC. Breast milk should start to be fortified once amounts greater than 100-120 ml/kg/day have been reached. A combination of probiotics that have proven efficacy and safety should be administered, regardless of the milk used and the centre's rate of NEC, beginning with the start of enteral feeding.

Given the above-mentioned measures, where the use of breast milk has independently been shown to have more relevance and better evidence, every effort should be made to have breast milk available from the start. Because there is no clear evidence on the start and it already exists for the use of breast milk, feeding may be delayed until it is possible to have breast milk or milk donated from a bank.

Acknowledgments

All the professionals that are part of the UGC Neonatology, whose daily work, effort and attitude have enabled this work to be carried out.

At the Human Milk Bank of the Hospital Virgen de las Nieves and Dr. Laura affumicato, who have made it possible for us to have donated human milk

Dr. Carlos Sierra and Dr. Joan Guzman for his invaluable contribution as external editors of the guide. A Drs Lin and Guthmann for their comments regarding the use of probiotics.

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