



Original / *Pediatría*

## New clinical practice guideline on enteral feeding in very low birth weight infants; first 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.

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### NUEVA GUÍA DE PRÁCTICA CLÍNICA SOBRE NUTRICIÓN ENTERAL DEL RECIÉN NACIDO DE MUY BAJO PESO AL NACIMIENTO; PRIMERA 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 medidas 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

Premature infants are born during what is a critical period for the growth and development of the nervous system. Nutrition for very low birth weight (VLBW) infants aims at promoting growth, similar to what takes place in utero, but without putting undue stress on metabolic and excretory functions. In practice this is difficult to achieve, not only because of difficulties posed by metabolic and digestive systems that are not fully developed, but also because of any intercurrent diseases an infant might have. In many cases the outcome is extrauterine growth restriction which often exacerbates prior intrauterine growth restriction.<sup>1</sup> Suboptimal nutrition during such a critical period can have irreparable consequences for growth and neurological development, and can cause diseases related to multiple metabolic syndrome to develop. 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). The literature shows high variability in NEC rates among centres, and with practices relating to how enteral feeding is started and continued with. This variability has been described in different countries, hospitals, and even among health professionals within the same hospital. It can be explained by the large degree of uncertainty surrounding many of the procedures we perform on a daily basis.<sup>2</sup>

As such, we decided to write a clinical practice guideline (CPG) on VLBW feeding that might provide answers for questions mainly about type of milk, optimal time to start feeding, how to administer feeding, and rate and amount recommended when making increases. This guideline was presented orally at a neonatology conference<sup>3</sup> and later in written form for the Paediatric Society of Eastern Andalusia.<sup>4</sup>

The first presentation did not include issues such as duration of fortification and whether or not probiotics are suitable—aspects which have led us to present the CPG, once updated, in a more complete manner.

The CPG is split into two parts. Methodology and search strategy and the questions about the time of onset and type of milk is presented in first.

In the second part answers to the rest of questions presented in the guide are thoroughly addressed.

## Scope & objectives of this guideline

This CPG is intended to help neonatologists make decisions about enteral feeding of VLBW infants in order to administer it safely and thus reduce the risk of NEC and postnatal growth restriction.

It addresses issues regarding type of milk, optimal time to start feeding, how to administer it, and rate and amount of increases. It also includes information on whether it is appropriate to continue fortification after hospital discharge or to use probiotics during the first weeks of life.

A second objective is to help reduce variability in daily practice among medical personnel.

## Methodology

CPGs may be defined as recommendations that are systematically developed to help health professionals and patients make the right decisions in specific clinical situations. Implementing them may improve quality of care by reducing variability and by streamlining the process of adding and agreeing on the use of new advances in health care practices.

### 1) Development strategy

There are three possible strategies for developing a CPG:

- a) Perform an exhaustive search of the CPGs published on the subject in question and, when one of high quality is found, use it as a benchmark to adapt the CPG based on our answers.
- b) Develop a CPG *de novo*, based on analysing information obtained from randomized clinical trials (RCTs), meta-analyses, observational studies, and so forth.
- c) Use a “mixed” strategy, where we start by selecting CPGs and doing systematic quality reviews (SQRs) that will be used to adapt and update the clinical issues similar to our initial formulation. For issues that have not been previously addressed, the *de novo* strategy will be used.

We have used this approach in our case. The criteria for selecting CPGs were the score from the Appraisal of Guidelines for Research and Evaluation (AGREE) and a publication date after January 2007. As for systematic reviews, the selection criterion was based on critical reading, applying the Critical Appraisal Skills Program Español (CASPe) methodology.

After making the selection, we evaluated whether the CPG and SQR adequately responded to the questions formulated. To do this, we checked whether the following criteria were fulfilled:

- Consistency among the answers provided by the various CPGs.
- Whether these answers needed to be updated.
- Level of recommendation and applicability of them.
- Whether there were Cochrane reviews.

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

*Levels of evidence*

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

*Grades of recommendation*

<b>A</b>	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>B</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+.
<b>C</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 2++.
<b>D</b>	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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- In addition, special emphasis was placed on analyzing the population and determining when each procedure was carried out and whether the result and subsequent recommendation was able to be extrapolated to other groups.

Depending on these criteria, it was decided whether the question was formulated *de novo* or whether it was updated. To do this, individual studies were used.

To grade the levels of evidence and strength of recommendations, the Scottish Intercollegiate Guidelines Network (SIGN) scale was used (table I).

*2) Research, evaluation and selection of scientific evidence*

The search was performed using a step-by-step approach. The inclusion criteria were:

- Documents written in any language.
- Published in the past 5 years.
- Focused on diagnosis and treatment.

**Step No. 1**

Search for position papers containing methodology for evidence-based medicine in order to update the guideline: Enteral feeding of VLBW infants.

The search was performed using synthesis tools: UptoDate licensed by the Andalusian Health e-Library (BV-SSPA), including the terms: enteral nutrition; premature infant. The "Approach to enteral nutrition in the premature infant" review and related topics were selected: "nutritional composition of human milk and preterm formula for the premature infant", "human milk feeding and fortification of human milk for premature infants", "breastfeeding the preterm infant", and EBSCO's DynaMed with the topic: feeding the premature infant.

**Step No. 2**

Search for previously drafted CPGs.

PubMed was searched using the following search protocol: (("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guidelines"[All Fields]) AND ("enteral nutrition"[MeSH Terms] OR "enteral nutrition"[All Fields])) AND ("infant, low birth weight"[MeSH Terms] OR "low birth weight infant"[All Fields]). Twenty (20) results were obtained, and no CPGs similar to the subject of the search were found.

We also searched specialized websites for CPGs: National Guideline Clearinghouse (NGC), CMA infobase, National Institute for Health and Clinical

**Table II**  
*Two examples of formulating PICO questions*

<i>Patients</i>	<i>Intervention/comparison</i>	<i>Results</i>
VLBW infants < 32 GA and/or < 1,500 g	Keeping nil by mouth <i>versus</i> starting trophic enteral feeding in first 24 hours of life.	It has not been proven that fasting reduces the risk of NEC.
VLBW infants < 32 GA and/or < 1,500 g	Continuous enteral feeding <i>versus</i> intermittent feeding by bolus.	No benefits or disadvantages have been shown that enable continuous or bolus feeding to be recommended.

Excellence (NICE), Guía Salud and TripDatabase, and found one guideline fulfilling the search criteria: “Alimentación enteral del recién nacido menor o igual a 32 semanas de edad gestacional” published by the Mexican National Centre for Health Technology Excellence<sup>5</sup>. Based on this, two further guidelines were found, accessible online.<sup>6,7</sup> Another was recently added.<sup>8</sup> In addition, one CPG specifically for the prevention and management of NEC was found<sup>9</sup>.

### Step No. 3

Search for systematic reviews and meta-analyses using the PubMed search filter for the terms “clinical queries/systematic reviews”, with a result of 12 articles. Search protocol on PubMed Clinical Queries: “enteral nutrition” AND “low birth weight”.

We also searched EMBASE using the term “systematic reviews” and obtained 7 results.

### 3) *Preparing the document and formulating questions*

Several health professionals were involved in preparing this document, and they practice at the Neonatal Unit of the Hospital Regional Universitario de Málaga. They were chosen based on experience in the field of neonatology and absence of conflicts of interest. 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.

To formulate the key questions this guideline intends to answer, we used the PICO format—patient, intervention, comparison, and outcomes (examples of PICO-based questions can be found in table II)—addressing 21 questions in all (table III).

With regard to assigning level of evidence and degree of recommendation, we followed a peer evaluation done by different members of the team. In case of discrepancies, a new evaluation was performed by a third person in the research group.

Dr Carlos Sierra Salinas, who has been chair of the Spanish Society of Paediatric Gastroenterology, Hepatology, and Nutrition, and D<sup>a</sup> Juana Guzmán Cabañas,

neonatologist at Hospital Reina Sofía and professor of paediatrics at the University of Cordoba, took part as external reviewers in research dedicated to premature infant nutrition<sup>10</sup>.

## Discussion

### *Fasting or trophic enteral feeding?*

NEC is a serious disease that is life-threatening and can cause serious after-effects. Prematurity and other factors that cause mesenteric ischemia have been associated with NEC (vascular redistribution in cases of intrauterine growth restriction, unstable haemodynamics, hypoxia, etc.). It usually occurs in premature infants who have already been fed through the gastrointestinal tract. For this reason, for many years high-risk children were made to fast; the thinking (with few evidence-based tests) was that by doing so, NEC could be prevented.

In addition, the early intake of food through the gastrointestinal tract favours its maturation and development. Given the challenge of improving gastrointestinal development and the risk of causing the onset of NEC, “trophic enteral feeding” (TEF) was opted for, which consists of providing minimal amounts of milk, maintaining the amounts for several days without increasing, or increasing them when tolerated but in a quantity which does not constitute a nutritional function ( $\leq 24$  ml/kg/day). In clinical trials, TEF has been shown to have beneficial physiological and clinical effects on an individual basis: it improves tolerance, shortens the time to full enteral feeding, improves postnatal growth, and reduces cases of jaundice and sepsis.<sup>11</sup>

The meta-analysis by Tyson<sup>12</sup> assessed the clinical effect of TEF in premature infants  $\leq 33$  weeks gestational age (GA) and with a birth weight of less than 1,500 g. It included 11 clinical trials that initiated TEF between the first and the eighth day of life, continuing it for 5-10 days. The control group was made to fast for the first 6-18 days after birth, though some could have water. The meta-analysis of the infants on TEF showed a decrease in total days needed to reach full enteral feeding (-2,6) and in hospital stay (-11,4) and in hospital stay. There was no increase in the figures for NEC (n = 650, RR = 1.16, 95% CI = 0.75, 1.79).

**Table III**

*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?

Another meta-analysis from 2009 compared starting trophic amounts early on (prior to the 4th day of life and continued for 7 days) with fasting for the first week after birth, demonstrating that TEF was safe (no increased risk of NEC was found). However, none of the TEF-related physiological or clinical benefits shown in previous trials was found.<sup>13</sup>

#### Summary of the evidence

**1+** In haemodynamically stable infants < 1,500 g, administration of amounts of milk less than 24 ml/kg/day, with no increases for one week, is as safe as fasting for the same period.

**1+** TEF shortens the time needed to reach full enteral feeding, when compared with prolonged fasting.

Most of the studies included in the meta-analysis started feeding between the 2nd and 4th day and not in unstable children; hence the results cannot be extrapolated to all groups.

#### Recommendations

**A** Prolonged fasting should be avoided. Instead, trophic enteral feeding should be started in all haemodynamically stable infants < 1,500 g and/or < 32 weeks.

**D** Feeding should not be started in haemodynamically unstable infants.

#### When to start?

There is some controversy surrounding the optimal time to start enteral feeding. When trying to define it, the result is less divisive. The best evidence comes from a meta-analysis comparing feeding with progressive amounts early on (before the 4th day) versus starting later (from the 5th-7th day), with no statistically significant differences in incidence of NEC or mortality between the two groups.<sup>13</sup> This meta-analysis has some significant limitations. It includes 5 trials

with a wide range of feeding regimens: two used TEF for 7 days before making the increases (making it impossible to discuss early enteral feeding). Eighty (80%) per cent of the patients included were small for their gestational age, and so the results could not be extrapolated to the proper weight results. (However, children with IUGR are at an increased risk of NEC compared with those who do not have IUGR and are of the same gestational age; thus the expected result would be better in those who are at the right weight.)

Henderson, in a multicentre case-control study of NEC risk factors, found no differences between the two groups with respect to the time to start feeding (2.9 days for the cases vs. 2.8 days for the control group).<sup>14</sup>

In our search strategy, we found no prospective studies addressing the start of enteral feeding from the first day of life. Most studies dealing with TEF include clinically and haemodynamically stable children who usually begin feeding on the second or third day. Thus the literature is oriented toward starting feeding in the first days of life, after the child is shown to be haemodynamically stable without vasoactive drugs. The availability of colostrum may be another criterion to consider in choosing the time to start feeding.

It has not been possible to demonstrate the safety of enteral feeding, neither with trophic amounts in unstable premature infants nor in those requiring inotropic drugs to maintain haemodynamics.

#### Summary of the evidence

**1-** There is no difference in the rate of NEC or gastrointestinal intolerance between starting feeding in the first four days (usually the 2nd to 4th day) or starting it after fasting for five days or more.

The group starting it early rarely begins on the first day of life. Most of the children included in the meta-analysis have IUGR. Haemodynamically unstable infants were excluded.

**2++** Case-control studies have not shown that age at starting enteral feeding is a risk factor for NEC.

We found no trials that specifically address the issue of whether or not to start enteral feeding on the first day of life. It may indeed be possible in groups with a low risk of NEC, in particular if they are breast-fed.

#### Recommendations

**B** In premature infants, feeding should be started within four days, beginning as soon as they become haemodynamically stable (i.e., stable without vasoactive drugs).

√ Despite there is little evidence of starting feeding on the first day, we think that after the first few hours after birth, if the infant is hemodynamically stable and with good perfusion and skin color, the onset of trophic

feeding with colostrum or bank milk may have more benefits than risks. However, we cannot offer trials to support this assumption.

*In certain situations, such as when breast milk is temporarily unavailable or for patients with IUGR or umbilical catheters, should the start of feeding be delayed?*

In the literature we found no studies comparing the start of enteral feeding with formula until the mother's milk was available with temporary fasting until it was available. Since there is no clear evidence on the start time and the use of breast milk, the authors consider that before prescribing the start of formula feeding, colostrum should be obtained if possible, which is often already present from the first day in the mammary glands.

There is controversy around the optimal time to start enteral feeding in infants with IUGR. Most protocols recommend being very cautious with these children, delaying the start of feeding in most cases. The existing studies often include patients who are additionally associated with other risk situations, such as reversal of end diastolic flow in the umbilical artery. However, in a retrospective study with 578 infants with IUGR, with and without altered flow in the umbilical artery, Soregalori found no differences in NEC rates between the two groups<sup>15</sup> (**evidence 2-**).

In a clinical trial that included only premature infants who were small for their gestational age and had an abnormal foetal Doppler ultrasound (absent or reversed end diastolic flow in the umbilical artery or evidence of foetal vascular redistribution), Leaf found no differences in NEC between groups that started feeding on the second day versus those who started on the sixth day<sup>16</sup> (**evidence 1+**).

With regard to umbilical catheters, it might be plausible to think that blood flow in the gastrointestinal tract would be affected.

The clinical trial by Davey found no differences in the development of NEC among children with an umbilical catheter who started feeding on the second day of life (when the catheter was still in place) and those who started 24 hours after the catheter was removed (mean age: 5 days)<sup>17</sup> (**evidence 1+**).

Boo<sup>18</sup> et al. did a prospective cohort study to cast light on the risk factors of feeding intolerance. Starting feeding in the first 72 hours of life in patients with an umbilical catheter did not increase the risk (**evidence 2+**).

#### Summary of the evidence

**2+** Children with IUGR and absent or reversed end diastolic flow in the umbilical artery had more NEC (OR: 2.13 CI: 1.49-3.03).

**1+** In premature infants < 35 weeks with IUGR, pathological Doppler findings, and with no history of vasoactive drugs, starting enteral feeding during the 2nd day vs. the 6th day does not change the risk of NEC and shortens the time needed to reach full enteral feeding.

**4** We found no evidence of the safety of starting feeding on the first day of life, nor in the presence of haemodynamic changes or those requiring vasoactive drugs.

**1+** No relationship was found between umbilical catheter site and risk of developing NEC.

**2+** In VLBW infants with an umbilical catheter, no relationship was found between catheter and digestive intolerance.

## Recommendations

**B** In infants with IUGR < 35 weeks, with absent or reversed end diastolic flow in the umbilical artery, and with no haemodynamic changes or other gastrointestinal risk factors, feeding should be started during the 2nd day of life.

✓ We do not recommend starting feeding on day one, when vasoactive drugs are being given, when there are haemodynamic changes, or if poor skin perfusion is observed.

✓ If breast milk is not available on the second day, consider delaying the start until the third day.

**C** Patients with umbilical catheters should receive enteral feeding unless they have other risk factors contraindicating the early start of feeding.

## What to use for feeding?

Various studies have shown donor breast milk to have a protective effect on NEC versus infant formula<sup>19</sup> (**evidence 1++**). There are no trials comparing breast milk with formula<sup>2</sup>. Fresh breast milk (not milk from the bank) reduces the rate of hospital-acquired infection. As such, the feeding of choice for premature infants is breast milk; if it is not available, we will use milk donated by the bank and, and finally infant formula for premature infants.

## Summary of the evidence

**1++** Infant formula leads to a higher risk of developing NEC than human milk from the bank.

Fresh breast milk (not milk from the bank) reduces the rate of sepsis compared with formula, and this beneficial effect is dose-dependent.

## Recommendations

**A** Wherever possible, start enteral feeding with colostrum or breast milk.

**A** If it is not available, start with donated human milk (milk from the bank).

✓ If breast milk is temporarily not available, evaluate whether to delay starting enteral feeding for a few hours until it becomes available.

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