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Nutritional practices in very low birth weight infants: a national survey

Miguel Sáenz de Pipaón[1], Ricardo Closa[2], María Gormaz[3], Marcos Linés[4], Eduardo Narbona[5], Gerardo Rodríguez-Martínez[6], José Uberos J[5], Carlos Zozaya[1] and María L. Couce[7]

[1]Neonatal Unit. Department of Neonatology. Hospital Universitario La Paz. Instituto de Salud Carlos III. Red de Salud Materno Infantil y Desarrollo-SAMID. Department of Pediatrics. Universidad Autónoma de Madrid. Madrid, Spain. [2]Neonatal Unit. Peediatrics Service. Universitat Rovira i Virgili. Reus, Tarragona. Spain. [3]Division of Neonatology. Hospital Universitario y Politécnico. Valencia, Spain. [4]Department of Neonatology. Hospital Vall d'Hebron. Barcelona, Spain. [5]Pediatric Service. Hospital Clínico San Cecilio. Granada, Spain. [6]Department of Pediatrics. Universidad de Zaragoza. Zaragoza, Spain. [7]Neonatal Unit. UDyTEMC. Department of Pediatrics. Health Research Institute of Santiago (IDIS). CIBERER. Complexo Hospitalario Universitario de Santiago de Compostela. Santiago de Compostela, A Coruña. Spain

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Corresponding author: María L. Couce. Neonatal Unit. UDyTEMC. Department of Pediatrics. Health Research Institute of Santiago (IDIS). CIBERER. Complexo Hospitalario Universitario de Santiago de Compostela. 15706 Santiago de Compostela, A Coruña. Spain

e-mail: maria.luz.couce.pico@sergas.es

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ABSTRACT

Background: Significant efforts have been made to improve the nutritional support of very preterm infants. Large surveys may help to know the nutritional practices for preterm infants in neonatal units and identify if they are in line with the current guidelines.

Methods: A multicentre nationwide web-based survey on clinical feeding practices in very low birth weight (VLBW) infants was conducted in tertiary neonatal hospitals that admit infants with a birth weight < 1,500 g and/or a gestational age of < 32 weeks.

Results: The questionnaire was completed by 53 units (response rate, 59%). Over 90% of the units surveyed start amino-acid administration immediately after birth and more than half use novel intravenous fish oil-based lipid emulsions. Enteral nutrition is started within 24 hours of birth in 65% of units and 86% of these are medium-sized or large. Feeding volumes are increased at a rate of 10-30 ml/kg/day in > 90% of units. Monitoring of serum phosphorus was measured more frequently than albumin ($p = 0.009$) or triglycerides ($p = 0.037$), but only 28% of centres regularly measure pre-albumin as a nutritional biomarker. Human milk fortification and iron supplementation, starting at four weeks of age, are almost universal. However, only 30% of units administer 800 IU/day of vitamin D. Nearly 50% of the units discharge infants on preterm formula.

Conclusion: Most Spanish neonatology units use early amino-acid supplementation and over half use novel fish oil-based lipid emulsions. Post-discharge nutrition practices and vitamin administration vary greatly.

Key words: Enteral nutrition. Intravenous lipid emulsions. Neonates. Parenteral nutrition. Vitamins.

INTRODUCTION

When infants are born prematurely, the nutrient supply that supports their growth during intrauterine life is suddenly interrupted. Nutrient intake must therefore be restored as quickly as possible to achieve a growth pattern mimicking foetal growth (1-3). Most infants with a very low birth weight (VLBW) remain in the Neonatal Intensive Care Unit (NICU) for a period of time that is equivalent to the third trimester of gestation. During this time, one of the goals of the NICU team is to provide infants with sufficient nutrition to achieve a growth velocity similar to that in the uterus. However, preterm infants are more susceptible to malnutrition and extrauterine growth retardation (EUGR) early in life, and are hence more likely to experience skeletal

mineral deficiencies (4), growth failure (5) and neuropsychological development restrictions later in life (6).

Inadequate nutrient intake in VLBW infants between birth and hospital discharge can cause significant growth failure due to energy, protein, fat and micronutrient deficiencies. Postnatal growth deficits are more common in smaller preterm infants, with one study reporting weights below the 10th percentile in the vast majority of infants weighing ≤ 1,000 g at 36 weeks' corrected age (7). In another study, 44% of premature infants accumulated a deficit of more than 1 SD in weight during their stay in the NICU, and the percentage of children with cumulative weight deficits of more than two SDs increased from 14% at birth to 55% at discharge; at least 50% of this variability was attributed to nutrition (8). In addition, recommended nutrition goals are frequently not achieved, especially in the first weeks of life, and therefore considerable nutrient deficits can be expected in a high percentage of VLBW infants (9).

The body composition of a premature infant with a birth weight < 1,000 g is made up of just 1% fat and 8% protein. The recommended energy intake for the first four days of life is therefore high, at 110 kcal/kg/day (10), although higher intakes are necessary in the case of sepsis or respiratory distress. Clinical studies have shown that improving nutritional intake reduces cumulative energy and protein deficits in preterm infants (11), which improves growth and neurodevelopment (12). In a study of 564 infants from six NICUs, variations in nutrition explained much of the difference observed in growth velocity between the units, even after adjusting for case mix and medical characteristics (13). The quality and quantity of daily nutritional intake are thus critical, particularly during the first weeks of life. Delivery of enteral nutrition may be delayed or interrupted due to a lack of guidelines or perceived contraindications. Surveys on trends in clinical practice have been proposed as a useful way of establishing the knowledge base and treatment intentions of clinicians. They not only provide a reference standard but can also help clinicians assess their practices and even possibly identify solutions for improving growth and reducing EUGR (14).

It remains unclear to what extent recommendations for early nutrition in NICU patients have been translated into clinical practice in Spain. The aim of the study was to evaluate and compare clinical feeding practices for very preterm infants in Spanish

neonatal units. Our findings may inform integrated clinical pathways or protocols that will help to improve growth outcomes by decreasing practice variability.

METHODS

In June 2016, a multicentre nationwide web-based survey was sent by e-mail to 90 tertiary neonatal units in Spain that admit infants with a birth weight of < 1,500 g and/or a gestational age of < 32 weeks. All the centers were level-III care units according to the minimum recommendations for neonatal care in Spain, including at least 2,000 births/year and requirements in infrastructure, material and technical resources to care for preterm infants of any gestational age (15). The number of neonates weighing < 1,500 g admitted per year was assessed per centre.

The questionnaire consisted of 54 multiple-choice and open-ended questions on neonatal care unit demographics; which growth charts/standards are used (up to 40 weeks of corrected age and afterwards); parenteral nutrition employed, including the initial and the peak protein reached, the maximum intravenous lipid intake and the use intravenous fat emulsions containing docosahexaenoic acid; enteral feeding, with questions about trophic enteral feeding (initiation and advancement of enteral feeds and when full enteral feeding is achieved); access to donor human milk; indications for and use of human fortifier; supplementation with oral vitamins; nutritional status by biochemical monitoring (analytical parameters and frequency of use) and post-discharge feeding (Supplementary Table I: https://xxxxxxxxxxxxxxxxxx).

The definitive survey questionnaire was developed under the guidance of a panel formed by nine members of the Nutrition Working Group Executive Committee of the Spanish Neonatal Society. The panel first reviewed the literature in order to establish the range of discussion topics, and then held a face-to-face meeting to choose the questionnaire items. They also reviewed the survey online. To internally validate the questionnaire, 26 Spanish pediatricians with current experience in the care of premature newborn infants were invited to participate in the study.

Statistical methods

Data were analysed using the statistical software program R (version 3.3.1., 2016) (16). Descriptive statistics are presented as numbers and/or proportions. Fisher's exact test

was used to detect statistical differences between the variables studied, and p values were corrected using the Benjamini-Hochberg procedure. Only corrected p values < 0.05 were considered to be statistically significant.

Ethics

This study was conducted according to the principles of the Declaration of Helsinki. Since this study did not involve human subjects/patients or handling of medical records, ethical approval was not required.

RESULTS

Response rate

Senior consultants from 53 level-III neonatal units from a total of 90 across Spain answered the survey; this represented a response rate of 59%.

Demographics of the participating units

The units that responded to the survey were classified according to the number of VLBW infants admitted annually: 72% admit 25-49 infants/year (small neonatal unit), 11% admit 50-100 infants/year (medium unit), and 17% admit > 100 infants/year (large unit).

Parenteral nutrition

Forty-nine units (92.4%) administer amino acids immediately after birth, with a starting dose of at least 2 g/kg/day administered in 80% of cases (39/49). This dose is progressively increased to a maximum ranging from 3 g/kg/day (1.8%) to > 4 g/kg/day (7.5%). Most units (73.6%) reach a maximum dose of 3.5-4 g/kg/day. No effect was found for unit size.

Twenty-five units (47%) administer a maximum of 3-3.5 g/kg/day of lipids during the first week of life, 21 (40%) administer a maximum of 2-3 g/kg/day, and a minority administer a maximum of 3.5-4 g/kg/day. The use of intravenous lipid emulsions varied considerably. Novel fish oil-based lipid emulsions were the first choice in over half of the units (Table I). Of the units that used other types of emulsions, 27% stated that

they used docosahexaenoic acid containing fat emulsions as a second choice depending on the patient's illness.

Carnitine is routinely added to parenteral nutrition for infants requiring prolonged nutrition (> 4 weeks) in just 16 units (30%); 7.5% of units reported that they occasionally individualise carnitine supplementation.

Enteral feeding

In the absence of contraindications, all the units start minimal enteral feeding within 48 hours of birth, and the vast majority (n = 48) use a maximum dose of 20 ml/kg/day. Of the 53 units, 65% start enteral feeding in the first 24 hours of life; this percentage is 86% (13/15) in medium or large units and 55% (21/38) in small units (p = 0.054). Most neonatologists in Spain seem to delay advancement of enteral feed volumes only if the preterm infant is severely ill. When asked specifically about the management of trophic enteral feeding in preterm newborn infants weighing < 1,000 g at birth, 60% of the units stated that they do not maintain minimum feed volumes for some days before advancing to full feeding rates. Only 21% and 15% of the units that answered the survey maintained minimal enteral feeding rates for 3 and 4-5 days, respectively. Own mother's colostrum, when available, is the starting milk of choice in 44% of the units.

Enteral feeding volumes are increased at a rate of 10-30 ml/kg/day in 49 units (92%), > 20 ml/kg/d in 25 units (47%), 10-20 ml/kg/day in 24 units (45%), and 5-10 ml/kg/day in just four units (7.5%). The vast majority of units (98%) achieve full enteral feeding (defined as 150 ml/kg/day, i.e., at least 120 kcal/kg/day) in the first 20 days of life, and 42% achieve it in the first ten days.

Donor human milk is available in 47% of the neonatal units surveyed and is used for different indications when own mother's milk is not available. In most cases (84%), it is used for infants with a birth weight < 1,500 g and/or a gestational age of < 32 weeks, although indications appear to be more restricted in certain units. For instance, it is reserved for infants weighing < 1,500 g at birth diagnosed with intrauterine growth restriction in 8% of units and for neonates weighing < 1,000 g at birth in another 8%. Nearly all of the units (49/53, 92%) always fortify human milk and 6% (3/53) do so sometimes. Figure 1 summarises human milk fortification practices in Spain.

Units that use preterm formula switch to standard term formula at different moments: 30% continue to use the preterm formula until the infant weighs 3 kg, while 15% and 21.5% wait until the infant is near term (36 weeks) or has reached full-term corrected age, respectively. Finally, 18% make the switch when the infant is discharged, regardless of weight or corrected age, and 15% use other options and/or combinations. Infants are discharged on preterm formula in 49% of units.

Probiotics

Most units (80%) do not use probiotics routinely. In those that do, mixed *Lactobacillus* and *Bifidobacterium* strains are much more common than *Lactobacillus* strains only (87.5% *vs* 12.5%).

Nutrition and growth surveillance

Growth surveillance during and after the neonatal period are guided by different regional-national or international standards. Practices vary greatly between centres, but up to 40 weeks' corrected age the Fenton Preterm Growth Chart, the growth curves described by Carrascosa et al. (17) and the Spanish Neonatal Society's (18) are the most widely used to evaluate weight gain and linear and head growth (by 41.5%, 30.2% and 11.3% of units, respectively). WHO's Growth Standards appear to be the most widely used system to assess infants after 40 weeks corrected age (45.3% of units) and the second most used growth curves are the Carrascosa's curves (reported by 43,4% of units).

Biochemical monitoring usually include serum phosphorus (100%), albumin (83%), urea (70%), and triglycerides (77%) measurement. On the contrary, only 28% of centres regularly measure pre-albumin as a nutritional biomarker (Table II). Phosphorus was measured significantly more frequently than either albumin ($p = 0.009$) or triglycerides ($p = 0.037$).

Vitamin and iron supplementation

All the units surveyed use vitamin D supplementation, but with varying doses; 33 units (62%) use the lowest recommended dose (400 IU/day), while 30% use the highest dose (800 IU/ day) according to European recommendations. The remaining units use doses

in between these limits. Enteral vitamin A supplementation appears to be relatively uncommon in Spain, and was reported by just 26% of units. The most common dose (used in 84% of cases) was 700-1,500 IU/kg/day. Routine plasma vitamin measurements are uncommon. Vitamin D levels are routinely measured in 25% of units and only 2.5% measure both vitamin D and vitamin A.

All the hospitals start iron supplementation in patients weighing < 1,000 g at four weeks of age. Once again, the doses vary among centres: 47% administer 4-6 mg/kg/day, 37% administer up to 3 mg/kg/day, and 16% administer a maximum of 2 mg/kg/day. Vitamin and iron supplementation are maintained after discharge by most physicians (96%). Iron is maintained until complementary nutrition is introduced (57.5%) or at least until iron stores are checked after three months of iron supplementation (31%). Vitamin supplementation, in turn, is usually continued for longer (up to 12 months of age in 80% of units).

DISCUSSION

This survey provides an extensive overview of current nutritional practices in VLBW infants in Spain, providing clinicians with the opportunity to compare their practices with those of their peers. Our study shows that clinicians largely coincided in the administration of amino acids immediately after birth (minimum dose of 2 g/kg/day and maximum of 3.5-4 g/kg/day) and the use of novel fish oil-based lipid emulsions.

Our findings can be considered to be broadly representative of Spanish practices as almost 60% of the units contacted answered the questionnaire. Parenteral nutrition over several days after birth is still the predominant mode of nutrition. Over 90% of Spanish neonatal units introduce early parenteral amino acids, compared with 24% to 54% of respondents in a recent systematic review of six surveys conducted between 2002 and 2012 in the United States (n = 2) and Europe (n = 4) (19).

We have not assessed lipid infusion within the first 48 hours of life as recommended, but concerns about possible long-chain polyunsaturated fatty acid (LC-PUFA) deficiency during the early weeks of life of very preterm infants can be addressed by considering the use of fatty-acid supplements that fulfil essential fatty acid and, possibly, LC-PUFA requirements (20). Lipid emulsions contain various amounts of medium-chain triglycerides (MCT), olive oil, and/or fish oil and are widely used in the

units we surveyed, contrasting with data from France, where the most widely used lipid emulsion was soy oil (50%) + MCT oil (50%) (SO-MCT). Our study shows that Spanish neonatologists are aware of the benefits of using fish oil-based lipid emulsions for DHA status (21), retinopathy of prematurity (22), oxidative stress (23), and pulmonary hypertension (24).

Carnitine is an important nutrient for the metabolism of long-chain fatty acids and is found in adequate supply in breast milk and commercial formulas. It is not present, however, in parenteral nutrition solutions. Carnitine deficiency in preterm neonates has been linked to poor weight gain, intolerance of parenterally administered lipids, and increased periodic breathing (25). According to our data, carnitine is less frequently added to parenteral nutrition solutions in Spain than in the USA (26).

The majority of units surveyed establish full enteral feeding early on, with 42% reaching full feeding rates within the first ten days of life. Rapidly growing preterm infants have high protein and energy requirements, and European guidelines recommend an enteral protein intake of 4.0-4.5 g/kg/day for infants < 1,000 g and 3.5-4.0 g/kg/day for infants weighing 1,000-1,800 g (27). The protein content of expressed breast milk is ≈1.1 to 1.3 g/100ml after the first three to four weeks. Recent meta-analyses have suggested slightly increased in-hospital growth rates for multi-nutrient fortification (28). When volume goals are 150 ml/kg/day, as in our case, fortification is needed to meet recommended intake. Most of the units (94%) use standard fortifiers to supplement human milk in the early stages of feeding. The early addition of breast milk fortifier may overcome the problem of low protein intake in the transition from parenteral to enteral feeding (3).

Optimal nutritional management is a challenge, particularly in the post-discharge period. Although feeding human milk after discharge has beneficial effects on cognition and long-term health, some preterm infants should consume supplemented milk to provide adequate nutrient supply (29). Furthermore, establishing breastfeeding is frequently problematic. There is great variability in practice regarding enteral nutrition after discharge by neonatal units.

It is important for neonatologists managing high-risk patients to regularly monitor biochemical markers for evidence of abnormal bone turnover and inadequate mineral intake in order to detect the early phases of impaired bone mineralisation. As

metabolic bone disease is usually asymptomatic in infants, diagnosis depends essentially on screening. Diagnostic criteria include clinical manifestations, radiological findings, biochemical markers, and bone mineral content measurements. Serum phosphorous levels are measured by all the units in our survey. Phosphorous concentration is correlated with bone mineral density and should be routinely tested. Albumin was the second most widely measured marker in our study. Unfortunately, the value of albumin as a marker of nutritional status is being increasingly debated.

Iron deficiency is the most common micronutrient deficiency worldwide. For extremely LBW infants, recent guidelines recommend starting iron supplementation two to four weeks after birth and continuing until six to 12 months of age depending on the diet (27). In our survey, some centres exceeded the recommendations of 2-4 mg/kg/day. In contrast to most other nutrients, there are no mechanisms for regulating iron excretion from the human body. Excessive iron supplementation in infants may increase the risk of infection, poor growth, and disturbed absorption or metabolism of other minerals, such as zinc and cooper (30).

The methodological limitations of using surveys to assess nutritional protocols have been previously discussed in detail (30), and it should be reiterated that while such surveys reflect the treatment intentions of neonatal care personnel, they might not reflect actual clinical practice in the absence of a chart review. In addition, there may be inherent bias in responses, as clinicians might have a particular interest in neonatal nutrition and, therefore, may be more knowledgeable about current recommendations. Thus, actual practice could be less optimal than findings suggest.

In conclusion, the results of our study based on a national survey of tertiary neonatal care units in Spain describe current nutritional protocols in VLBW infants. Neonatologists' understanding and knowledge of the nutritional needs of preterm infants have improved compared to previous national surveys published. The introduction of amino-acid supplementation is in line with recent guideline recommendations in the majority of units, although carnitine supplementation is still relatively uncommon. Our survey shows that new fish oil-based lipid emulsions are the most widely used emulsions in Spanish neonatal care units. Enteral nutrition should be optimised. Initiation and gradual advancement of nutrition vary according to hospital practices, prescriber knowledge, and progress in the understanding of the nutritional

needs of VLBW infants. The clinical benefits of lipid emulsions of varying oil composition over conventional pure soybean oil emulsions need to be further investigated. There is a need for standardisation of feeding guidelines and evidence-based enteral feeding strategies to optimise enteral nutrition after discharge.

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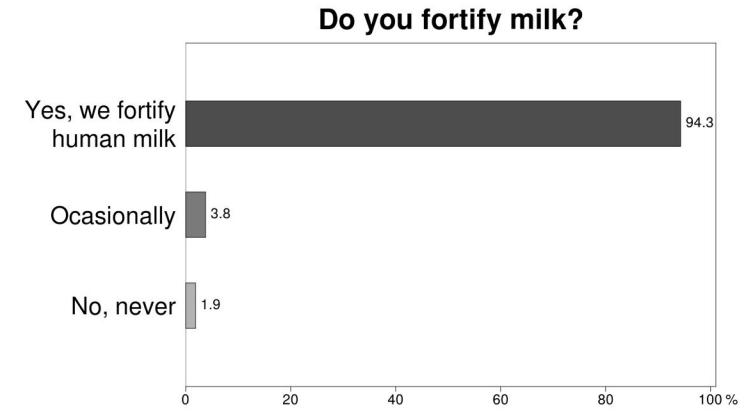
Table I. First-choice intravenous lipid emulsions (%)

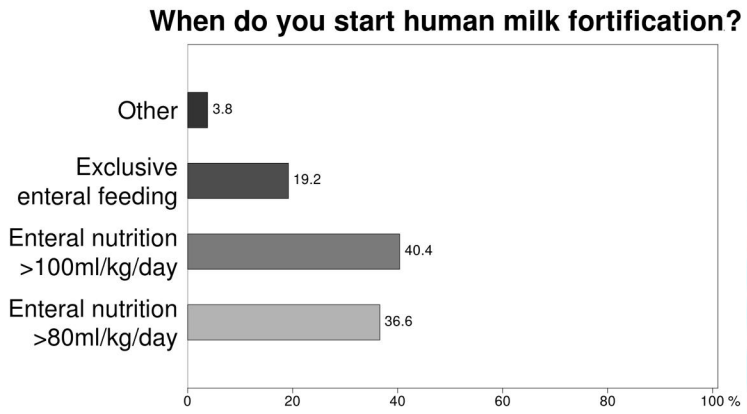
Lipid emulsion		
Composition	Units (%)	Fish oil
Soy oil (100%)	15.4%	No (46.2%)
Soy oil (50%) + MCT oil (50%)	13.5%	
Olive oil (80%) + soy oil (20%)	17.3%	
Soy oil (40%) + MCT (50%) + fish oil (10%)	5.8%	Yes (53.8%)
MCT oil (30%) + olive oil (25%) + soy oil (30%) + fish oil (15%)	48%	

Table II. Nutritional biomarkers: frequency of determination

	Daily	*Weekly*	*Fortnightly*	*Monthly*	*Individualized (depending on patient's status)*	*Other*
Albumin	-	19.1%	*46%*	6.3%	23.8%	4.8%
Pre-albumin	-	8.3%	*45.8%*	4.2%	37.5%	4.2%
Phosphorus	2.5%	24.1%	*40.5%*	10.1%	19%	3.8%
Urea nitrogen	-	*44.6%*	*25%*	3.6%	26.8%	-
*Triglycerides**		14%	*42.1%*	-	35.1%	7%

*1.8% measure triglycerides whenever intravenous fat delivery is increased (not included in "Other" category).





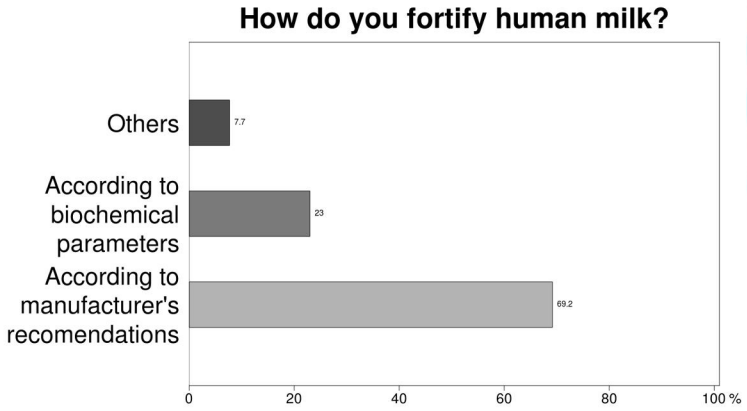


Figure 1. Human milk fortification practices in Spanish neonatal units.

Supplementary Table I. Web-based questionnaire used in the survey of nutritional practices in premature newborn infants with a gestational age < 32 weeks and/or a birth weight < 1,500 g admitted to Spanish Neonatal Intensive Care units.

Hospital/address

1.1 How many infants < 1,500 g at birth are admitted to your unit per year?

Growth assessment

1.2 Which growth charts/standards do you use to calculate percentiles up to a gestational age of 40 weeks?

1.3 Which growth charts/standards do you use after a post-gestational age of 40 weeks?

Parenteral nutrition

2.1. Do you use standardized starter parenteral nutrition?

2.2. If so, what is the initial protein supply (g/kg/day)?

2.3. What is the peak protein (g/kg/day) reached during parenteral nutrition?

2.4. In the first week of life, what is the maximum intravenous lipid intake (g/kg/day) achieved?

2.5. Do you use intravenous fat emulsions containing docosahexaenoic acid (DHA)?

2.6. In case of routine or variable use of these intravenous fat emulsions, please provide the name of the product you use.

2.7. Do you supplement carnitine in the case of prolonged parenteral nutrition (> 4 weeks)?

Enteral feeding

3.1. How soon do you initiate trophic enteral feeding (in the absence of specific contraindications)?

3.2. What is the usual initial volume of enteral trophic nutrition (ml/kg/day)?

3.3. In preterm infants with a birth weight between 1,000 and 1,500 g, how long do you maintain trophic enteral feeding before advancing?

3.4. How long does the trophic feeding phase last in infants with a birth weight < 1,000 g?

3.5. At what rate do you advance enteral feedings (ml/kg/day)?

3.6. When, on average, does a premature infant (< 1,000 g at birth) reach full enteral feeding in your unit? (Consider full enteral feeding to be 120 kcal/kg/day with at least 150 ml/kg/day)

3.7. In the case of formula feeding, how long do you keep preterm formula for premature babies in extremely premature infants?

Human milk fortification

4.1. Do you fortify human milk if used to feed premature newborns?

4.2. If so, please indicate the name(s) of the product(s) used.

4.3. If you fortify human milk, when do you start to do this?

4.4 How long do you fortify human milk for?

4.5. How do you fortify human milk? (According to the manufacturer's instructions, blood and/or milk biochemical parameters)

4.6. If you fortify human milk according to blood and/or milk biochemical parameters, do you sometimes increase the fortifier concentration above the manufacturer's recommendations?

4.7. If you fortify human milk according to blood and/or milk biochemical parameters, do you occasionally use modular supplements (protein, carbohydrate, fat)?

4.8. If you use modules, please indicate the name(s) of the product(s) used.

4.9. In the case of breast milk feeding (own mother's milk), do you use colostrum when available to optimize nutrient supply?

Human donor milk

5.1. Can enteral feeding be started with human donor milk in your unit?

5.2. If so, considering gestational age and/or birth weight, what are the indications in

your unit?

Probiotics

6.1. Do you use probiotics on a regular basis?

6.2. If yes, which species/strains do you use?

Nutritional status/biochemical monitoring

Do you measure:

7.1. Urine nitrogen?

7.2. If so, how often?

7.3. Phosphorus?

7.4. If so, how often?

7.5. Albumin?

7.6. If so, how often?

7.7. Pre-albumin?

7.8. If so, how often?

7.9. Triglycerides?

7.10. If so, how often?

Vitamin and mineral supplementation

8.1. Do your patients receive enteral vitamin D supplementation from the second week of life?

8.2. If so, what is the dose?

8.3. Do you routinely monitor vitamin D and vitamin A levels?

8.4. Do you supplement with enteral vitamin A?

8.5. If so, how much?

8.6. Do preterm infants with a birth weight < 1,000 g receive iron supplements from the age of four weeks in your unit?

8.7. If so, at what amount?

8.8. When the hospital discharges the infant, do you continue to prescribe iron, multivitamin, or vitamin D supplements?

8.9. How long do you prescribe iron supplements for?

8.10. How long do you prescribe vitamin supplements for?

Nutrients and energy requirements

9.1. Do you estimate/evaluate macro and or micronutrient supply?

9.2. If so, how often?

9.3. How do you do this?

9.4 If you use a standardized method, please indicate which.