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GUIDELINES

Guidelines for enteral nutrition in infants born preterm: 2023 update by the Portuguese Neonatal Society. Part I. Nutrient requirements and enteral feeding approach during the hospital stay

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Abstract

Recent evidence-based data motivated this update of the Portuguese Neonatal Society guidelines for the enteral nutrition of infants born preterm. The purpose of this document is to support the clinical practice and was mainly oriented by the updated European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) 2022 position paper, the World Health Organization recommendations 2022, and other reference articles, particularly systematic reviews. These guidelines are published in two parts. Part I addresses the nutrient requirements and the enteral feeding approach during the hospital stay, including optimization of the mother's own milk feeding and methods for enteral feeding. Part II is directed to particularities of enteral feeding in specific clinical conditions, and feeding after discharge, including breastmilk fortification at home and introduction of complementary feeding.

Keywords: Enteral nutrition. Formula feeding. Human milk fortification. Nutrient requirements. Preterm infants.

Recomendações para a nutrição entérica na criança nascida pré-termo: atualização em 2023 da Sociedade Portuguesa de Neonatologia. Parte I. Necessidades nutricionais e nutrição entérica durante o internamento

Resumo

Dados recentes baseados na evidência motivaram esta atualização das recomendações da Sociedade Portuguesa de Neonatologia para a nutrição entérica de crianças nascidos pré-termo. O objetivo deste documento é apoiar a prática clínica e é orientado principalmente pela atualização da posição da European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) de 2022, das recomendações da Organização Mundial de Saúde de 2022 e outros artigos de referência, sobretudo

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revisões sistemáticas. Estas recomendações são publicadas em duas partes. A Parte I, aborda as necessidades nutricionais e a abordagem da nutrição entérica durante o internamento, nomeadamente a otimização do leite da própria mãe e os métodos para administrar a nutrição entérica. A Parte II, foca-se nas particularidades da nutrição entérica em situações clínicas especiais e na alimentação após a alta, incluindo a fortificação do leite materno no domicílio e a introdução e da diversificação alimentar.

Palavras-chave: Nutriçao entérica. Fórmula láctea. Fortificação do leite humano. Necessidades nutricionais. Recém-nascido pré-termo.

Introduction

The first guideline (formerly known as "Consensus") of the Portuguese Neonatal Society for neonatal enteral nutrition was published in 2004[1]. In 2014, that guideline was updated specifically for infants born preterm[2] and was mainly oriented by the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) 2010 position paper[3]. Meanwhile, new evidence-based data was published, motivating this further review, oriented by the updated ESPGHAN 2022 position paper[4], the WHO recommendations 2022, recent recommendations from other scientific bodies[5-7], and relevant reference articles, particularly systematic reviews.

This guideline is divided into two parts: I) nutritional requirements of preterm infants; enteral nutrition aspects during hospital stay, including when and how to initiate enteral feeding, how to advance, modes of feeding, methods of human milk (HM) fortification, preterm formulas, and nutrition in particular conditions; and II) feeding after discharge, including breastfeeding, formula feeding, and introduction of complementary feeding.

Specific recommendations of the Portuguese Neonatal Society have been published on enteral supplementation of multivitamins and trace elements for newborn infants[8] and growth charts to assess growth in preterm infants[9], therefore these topics are not addressed in this guideline.

Recommendations are graded according to levels of evidence - LOE (in descending order 1-4) and grades of recommendation - GOR (A - strong recommendation, B - recommended, C - conditional recommendation, and GPP - good practice points/expert consensus) [4]. The LOE 1 and 2 are further sub-classified as 1++, 1+, 1-, 2++, 2+, and 2-, depending on the quality of the studies[4].

To support the practical routine, Tables 1 to 3 for rapid consultation of main aspects of preterm enteral feeding are provided at the end.

Gastrointestinal immaturity

According to gestational age, preterm infants are classified as extremely preterm (< 28 weeks), very preterm (28-31 weeks), and moderate or late preterm (32-36 weeks)[10].

The less mature the infant, the less the production of gut digestive enzymes and growth factors, and the more immature the enteric autonomic nervous system[11]. Consequently, in less mature infants feeding difficulties are expected, that include longer time to improve gastrointestinal motility, delay in gastric emptying and even reverse peristalsis, abdominal distension, and bacterial overgrowth[11]. Additionally, in more immature infants, the gastrointestinal barrier is impaired during the first postnatal weeks, associated with less milk-degrading microbes and more bacterial oxidative stress proteins[12]. These factors combined with reduced mucus thickness, lower intestinal alkaline phosphatase secreted by enterocytes, and diminished secretion of lysozymes by Paneth cells, increase the risk of inflammation, dysbiosis, and development of necrotizing enterocolitis (NEC)[13].

On the other hand, the premature infant intestine seems to respond to postnatal exposure to nutrients, promoting absorption, intestinal motor response, and secretion of gastrointestinal hormones and peptides[11,14].

Recommended enteral nutrient intakes

The recommended enteral intakes herein stated primarily concern stable fully enterally fed preterm infants. The recommended enteral intakes for fluid, macronutrients, mineral, and electrolyte intake are summarized in Table 1, for trace elements, water-soluble vitamins, and fat-soluble vitamins intake in Table 2, and for enteral nutrition approach and procedures during the hospital stay in Table 3.

Fluid

Fluid intake of 150-180 mL/kg/day is recommended in stable infants (GOR B)[4].

In infants fed non-fortified MOM, enteral fluid intakes of up to 200 mL/kg/d may be safe (GOR GPP)[4,15].

Fluid intake as low as 135 mL/kg/day seems sufficient to maintain body homeostasis and safe to avoid renal compromise[4].

In infants with bronchopulmonary dysplasia (BPD) or with significant patent ductus arteriosus (PDA), fluid restriction is usually necessary, preferably around 135 ml/kg/day (GOR GPP), but it can be increased to 150 ml/kg/day if tolerated[16,17].

Table 1. Recommended intakes of fluid, macronutrients, minerals, and electrolytes in stable full enterally fed preterm infants, after the first postnatal week[4]

Nutrient	Observations	Daily intake (per kg)	GOR
Fluids (mL)	Stable infants	150-180	B
	BPD and PDA	135-150	GPP
	Non-fortified MOM	Up to 200	GPP
Energy (kcal)	Stable infants	115-140	A
	BPD	120-150	GPP
	Suboptimal growth	140-160	B
Protein (g)	Very preterm infants	3.5-4.0	A
	Suboptimal growth	Up to 4.5	A
PER (g/100 kcal)		2.8-3.6	B
Fat (g) ARA (mg) DHA (mg)	With sufficient ARA	4.8-8.1 30-100 30-65	B B A
Carbohydrate (g)		11-15	B
Ca (mg)		120-200	C
P (mg)		70-115	C
Ca: p ratio (mg: mg)		≤ 1.8	C
Mg (meq)	Fed fortified HM or preterm formula	0.4-0.5	C
Na (mEq)		3.0-8.0	GPP
Cl (mEq)		3.0-8.0	C
K (mEq)		2.3-4.6	B

Grade of recommendation (GOR), in descending order: A - strong recommendation, B - recommended, C - conditional recommendation, and GPP - good practice points[4].
BPD: bronchopulmonary dysplasia; HM: human milk; PDA: patent ductus arteriosus; PER: protein-to-energy ratio.

Energy

A total energy intake of 115-140 kcal/kg/day is recommended in most stable infants (GOR A).

In infants with BPD[16] and/or suboptimal growth, more than 140 kcal/kg/day may be necessary, provided it does not exceed 160 kcal/kg/day and guarantees the recommended protein-to-energy ratio (PER) (GOR B)[4] stated below.

Protein and protein-to-energy ratio

In very preterm infants, protein intake of 3.5-4.0 g/kg/day (GOR A) and a PER of 2.8-3.6 g/100 kcal are recommended (GOR B)[4].

In exclusively enterally fed infants, reduction of protein intake should be considered if serum urea exceeds 34 mg/dL (BUN > 16 mg/dL), in the absence of fluid or renal derangements[4].

In infants with suboptimal growth, protein intake may be increased to 4.5 g/kg/day (GOR A) provided serum urea is < 34 mg/dL (blood urea nitrogen - BUN < 16 mg/dL) and that other causes justifying poor growth have been excluded (GOR C)[4].

Fat

Total fat intake of 4.8-8.1 g/kg/day is recommended (GOR B)[4].

Medium chain triglycerides should be < 40% of total fat intake (GOR B)[4].

Fatty acids intake should be in the range of linoleic acid (LA) 385-1540 mg/kg/day, α-linolenic acid (ALA) > 55 mg/kg/d, LA: ALA ratio (in mass) 5-15:1 (GOR B), arachidonic acid 30-100 mg/kg/day (GOR B), docosahexaenoic acid 30-65 mg/kg/day (GOR A), and eicosapentaenoic acid < 20 mg/kg/d (GPP)[4].

Table 2. Recommended intakes of trace elements, water-soluble vitamins, and fat-soluble vitamins in stable full enterally fed preterm infants, after the first postnatal week[4]

Nutrient	Observations	Daily intake (per kg)	GOR
Trace elements			
Iron (mg)	From 2 weeks, in very preterm infants	2.0-3.0	A
	During erythropoietin treatment	Up to 6.0	B
Zinc (mg)		2.0-3.0	GPP
Cooper (μg)		120-230	GPP
Iodine (μg)		11-55	GPP
Selenium (μg)		7-10	GPP
Manganese (μg)		1-15	GPP
Chromium (μg)		0.03-2.25	GPP
Molybdenum (μg)		0.3-5	GPP
Water soluble vitamins			
Thiamine (B_1) (μg)		140-290	GPP
Riboflavin (B_2) (μg)		200-430	GPP
Niacin (B_3) (mg)		1.1-5.7	GPP
Pantothenic acid (B_5) (mg)		0.6-2.2	GPP
Pyridoxine (B_6) (μg)		70-290	GPP
Biotin (B_7) (μg)		3.5-15	GPP
Ascorbic acid (C) (mg)		17-43	GPP
Cobalamin (B_{12}) (μg)		0.1-0.6	GPP
Fat soluble vitamins			
Vitamin A (retinol) (IU)		1333-3300	B
Vitamin D (calciferol) (IU)		400-700, maximum 1000	B
Vitamin E (tocopherol) (mg)		2.2-11	B
Vitamin K (phytomenadione) (μg)		4.4-28	B

Grade of recommendation (GOR), in descending order: A - strong recommendation, B - recommended, C - conditional recommendation, and GPP - good practice points[4].
HM: human milk; BPD: bronchopulmonary dysplasia; PER: protein-to-energy ratio; PDA: patent ductus arteriosus.

Table 3. Enteral nutrition approach and procedures during the hospital stay[4]

Procedure	Observations	GOR
Early colostrum administration	Administer mother's own colostrum within the first 48 postnatal hours, in the mouth or in the oropharynx	
Type of feeds	1st choice: fortified MOM, preferably fresh MOM, or previously frozen MOM	A
	2nd choice: fortified DHM	B
	3rd choice: preterm formula, if MOM and DHM are not available	
Nasogastric vs. orogastric tube feeding	No evidence exists to prefer any mode of feeding and local preferences are allowed	
Starting volume of feeds	Start with 12-24 ml/kg/day, preferably using MOM or DHM	B
Advancing volume of feeds	Advance 18-30 mL/kg/day in stable preterm infants, especially if MOM is used	A
Bolus vs. continuous feeding	Any method can be used, with bolus feeding slightly superior to continuous feeding	
Pacifier use	Non-nutritive sucking a pacifier during tube feeding may have benefits	
Oral feeding	Oral feeding may be started from 32 weeks PMA, depending on the competence and stability of the infant	GPP
Gastric residuals	Routine monitoring of gastric residuals is not recommended in clinically stable infants	B
Human milk fortification	Start fortification using a multi-nutrient fortifier when HM intake reaches 40-100 mL/kg/d	C
	Either adjustable or targeted fortification, may be appropriate in alternative to standard fortification	A

Grade of recommendation (GOR), in descending order: A - strong recommendation, B - recommended, C - conditional recommendation, and GPP - good practice points[4].
DHM: donor human milk; HM: human milk; MOM: mother's own milk; PMA: post-menstrual age.

Carbohydrates

Carbohydrate intake of 11-15 g/kg/day is recommended (GOR B)[4].

Higher carbohydrate intake may be considered for a short period of time to facilitate catch-up growth (GOR GPP)[4].

Minerals

Mineral intakes should be: calcium 120-200 mg/kg/day (3.0-5.0 mmol/kg/day), phosphorus 70-115 mg/kg/day (2.2-3.7 mmol/kg/day), Ca: p ratio ≤ 1.8 (in mass) or ≤ 1.4 (molar), and magnesium 9.0-12.5 mg/kg/day (0.12-0.21 mmol/kg/day or 0.4-0.5 mEq/kg/day) (GOR C)[4].

Infants fed preterm formula may require higher mineral intakes than those fed HM (GOR GPP)[4].

Electrolytes

Sodium. An intake of 3-8 mEq/kg/day (3-8 mmol/kg/day) is recommended (GOR GPP)[4]. The upper limit of sodium intake should be considered in infants receiving upper limit of energy and protein intakes or with important sodium loss[4]. Sodium supplements added to milk or formula should be divided among feeds administered over 24 hours (GOR C)[4].

Potassium. An intake of 2.3-4.6 mEq/kg/day (2.3-4.6 mmol/kg/day) is recommended (GOR B)[4]. In exclusively enterally fed preterm infants, potassium requirements are linearly associated to protein retention (LOE 3), therefore the upper limit of potassium intake should be considered in growing infants receiving upper limits of energy and protein intakes (GOR B)[4].

Chloride. An intake of 3-8 mEq/kg/day (3-8 mmol/kg/day) is recommended (GOR C)[4]. Chloride intake should be slightly lower than the sum of sodium and potassium intakes to avoid metabolic acidosis (GOR B)[4]. When oral salt supplementation is necessary, high intakes of sodium or potassium should be accompanied by high chloride intake (LOE 2++)[4].

Trace elements

Iron. In very low birth weight (VLBW) infants, iron intake of 2-3 mg/kg/day is recommended, starting at 2 postnatal weeks (GOR A)[4]. In these infants, regular measurements of serum ferritin are recommended during the hospital stay (LOE 1-) (GPP)[4]. Iron intakes of 3-4 mg/kg/day, up to the maximum of 6 mg/kg/day, may be needed over a limited period in infants treated with erythropoietin (GOR B) or if serum ferritin is < 35-70 μg/L (GOR GPP)[4]. If ferritin is > 300 μg/L, discontinuation of iron supplementation should be considered (GOR GPP)[4]. Prolonged iron intake > 3 mg/kg/day should be avoided (GOR B) as iron is a reactive pro-oxidant and an important substrate for pathogens (LOE 1-)[4].

Zinc. An intake of 2.0-3.0 mg/kg/day is recommended (GPP)[4]. Measurement of serum zinc should be considered in infants with dermatitis or poor growth and low alkaline phosphatase levels, especially if associated with excessive gastrointestinal fluid losses (GPP)[4].

Cooper. An intake of 120-230 μg/kg/day is recommended (GPP)[4].

Iodine. An intake of 11-55 μg/kg/day is recommended (GPP)[4].

Selenium. An intake of 7-10 μg/kg/day is recommended (GPP)[4].

Manganese. An intake of 1-15 μg/kg/day is recommended (GPP)[4].

Chromium. An intake of 0.03-2.25 μg/kg/day is recommended (GPP)[4].

Molybdenum. An intake of 0.3-5 μg/kg/day is recommended (GPP)[4].

Water soluble vitamins

Thiamine (B_1). An intake of 140-290 μg/kg/day is recommended (GPP)[4].

Pantothenic acid (B_5). An intake of 0.6-2.2 mg/kg/day is recommended (GPP)[4].

Biotin (B_7). An intake of 3.5-15 μg/kg/day is recommended (GPP)[4].

Niacin (B_3). An intake of 1.1-5.7 mg/kg/day is recommended (GPP)[4].

Ascorbic acid (C). An intake of 17-43 mg/kg/day is recommended (GPP)[4].

Riboflavin (B_2). An intake of 200-430 μg/kg/day is recommended (GPP)[4].

Pyridoxine (B_6). An intake of 70-290 μg/kg/day is recommended (GPP)[4].

Folate. An intake of: 23-100 μg/kg/day is recommended (GPP)[4].

Cobalamin (B_{12}). An intake of 0.1-0.6 μg/kg/day is recommended (GPP)[4].

Fat soluble vitamins

Vitamin A (retinol, retinoic acid). An intake of 1333-3300 IU/kg/day is recommended (400-1000 μg retinol ester/kg/day) (GOR B)[4].

Vitamin D (calciferol). An intake of 400-700 IU/kg/day up to the maximum of 1000 IU/kg/day is recommended (GOR B)[4].

Vitamin E (tocopherol). An intake of 2.2-11 mg/kg/day is recommended (GOR B)[4].

Vitamin K (phytomenadione). An intake of 4.4-28 μg/kg/day, is recommended (GOR B)[4].

Types of feeds

Mother's own milk

A systematic review and meta-analysis of energy and macronutrient content of preterm MOM, at various lactation periods, found that protein content is reduced by half within 10-12 weeks of lactation and fat content increases over time[18].

The MOM contains non-nutritional factors, including oligosaccharides, hormones, growth factors, enzymes, immunoglobulins, antioxidants, cytokines, cellular components, and beneficial microbes, providing relevant biologic benefits[4,19,20]. Several bioactive factors are higher in preterm breastmilk compared to full-term breastmilk[19].

In a follow-up study, it was found that breastfeeding is shorter than recommended in Portuguese very preterm infants enrolled in the EPICE cohort, a research group in which Portugal is included[21]. This study also included a systematic review concluding that this problem is common globally[21].

The World Health Organization[20], the Baby-Friendly Hospitals Initiative[5] and data of very preterm infants from the EPICE Research Group[22-24] have pointed out critical steps for the success of exclusive breastfeeding, and the following deserving emphasis:

- Institution-based multidisciplinary interventions to promote HM feeding should include educational and breastfeeding support programs[5,21,24];
- A written breastfeeding policy should be routinely communicated to all healthcare staff[5];
- The training and acquisition of specific knowledge and skills by the healthcare staff are essential for intervention on the mothers, concerning lactation, breastmilk extraction, and breastfeeding support[5,20];
- Receiving MOM as first enteral feed is of crucial importance[5,20];
- Promoting parental presence and their involvement in care increases the likelihood of successful breastfeeding at discharge[23];
- In sufficiently stable preterm infants, early, continuous, and prolonged skin-to-skin contact (kangaroo parent care) should be encouraged[5,20,24];
- Units using donor human milk (DHM) have higher rates of exclusive breastfeeding at discharge[22].

To maximize milk supply, mothers should begin to express breastmilk within 3-6 hours[25] following delivery (LOE 2-), or even earlier[26]. Initially, expressing breastmilk 8-12 times per day is desirable[27]. Afterwards, at least 5 daily pumping sessions is suggested to support mothers of hospitalized preterm infants[28]. Electric pump is preferred, since this method can mimic the biphasic infant suckling, increasing prolactin and oxytocin and milk production, compared to manual expression[26,27]. Double electric pump is reported to produce larger volumes of milk than single electric pump[26].

Despite potential adverse consequences of postnatally acquired citomegalovirus in more immature infants, there is insufficient evidence to recommend routine pasteurization of MOM from citomegalovirus positive women (GOR B), as pasteurization inactivates or destroys several components, such as growth hormones, digestive enzymes, and immunological and bioactive factors (LOE 1++)[4].

In brief, fresh mother's own milk (MOM) is recommended as the first choice to feed preterm infants, provided it is fortified as recommended (GOR A)[4,7,20,29]. If fresh MOM is not available, previously frozen milk in the same sequence in which it was expressed should be used[29]. Starting to express breastmilk 3-6 hours following delivery with an electric pump maximize the milk supply (GPP). There is insufficient evidence to recommend routine pasteurization of MOM from citomegalovirus positive women (GOR B).

Donor human milk

DHM is usually expressed from women who delivered term born infants a few months before; it has lower macronutrient and bioactive factor contents compared to milk expressed at earlier stages (Embleton 2023). In particular, at 4 weeks of lactation the protein content in single or multiple DHM pools is lower than that of MOM (de Halleux 2013). Holder-pasteurization eliminates citomegalovirus but inactivates or destroys several aforementioned components (LOE 1++)[4].

It is recommended that when MOM is not available, the second choice for preterm infants is fortified DHM, conditionally recommended over preterm formulae (GOR B)[4,20].

Preterm formula

Preterm formulae are intended to be used in growing preterm infants during the hospital stay, providing

nutrient intake that match their high requirements. These formulae have higher energy, macronutrients, minerals, vitamins, and trace elements compared with term infant formulas, and include: energy 80-82 kcal/100 mL, protein 2.4 g/100 mL (3 g/100 kcal), carbohydrates 8.6 g/100 mL, fat 4.3 g/100 mL, calcium 133-146 mg/100 mL (165-180 mg/100 kcal), and phosphorus 67-81 mg/100 mL (83-100 mg/100 kcal)[30,31].

While in hospital, it is preferable to use preterm formulae in liquid form than in powder as ready-to-use liquid form reduces the risks related to errors in formula reconstitution and bacterial contamination, considering that industrial milk formulas are not sterile[32].

It is recommended that when MOM and DHM are not available, preterm formula should be preferred (GOR A)[4,29], particularly in infants < 32 weeks of gestation (GOR C)[20].

Hydrolyzed protein formula

Hydrolyzed protein formulae may accelerate gastrointestinal transit and enteral feeding advancement, but there is no evidence to support that their use improves long-term outcome (LOE 1+)[4].

Hydrolyzed protein formulae may be used for early feeding in preterm infants when HM is not available (GOR B)[4].

Post-discharge formula

Post-discharge formulae have a nutrient content ranging between preterm formulae and term infant formulae, including energy 71-74 kcal/100 mL, protein 1.8-1.9 g/100 mL, and average of carbohydrates 7.6 g/100 mL, fat 4.0 g/100 mL, calcium 80 mg/100 mL, and phosphorus 50 mg/100 mL[30,31,33].

It is recommended that post-discharge formulae are used after discharge in infants born < 33 weeks gestation, when HM is insufficient or not available (GOR B)[34].

Enteral nutrition during the hospital stay

Recommendations for enteral nutrition in stable preterm infants, during hospital stay, are described below and summarized in Table 3.

A main reason for the heterogeneity in enteral nutrition practices in preterm infants is the fear of NEC related to the intestinal immaturity[11]. Enteral nutrition in preterm infants improves if the approach is standardized based on current evidence, namely when and how to start, how to administer (continuously or intermittently), what to administer (MOM, donor human milk – DHM or formula), how to progress (volume) and when to interrupt or reduce (GOR B)[4].

Oral/oropharyngeal colostrum administration

Evidence exists that mother's own colostrum has immunomodulatory effects on the preterm infants, including the increased absorption of sIgA and lactoferrin[35], although related clinical advantages need evaluation and evidence. Systematic reviews and meta-analyses[36,37] assessed the effect of oral or oropharyngeal colostrum administration within the first postnatal hours or days in preventing mortality and morbidity in preterm infants. It was concluded that no adverse effects were associated with this procedure that seemed to shorten the time to achieve full enteral feeds, however without clear advantages in reducing the risk of late-onset infection, NEC, pneumonia, chronic lung disease, retinopathy of prematurity, or death before discharge (LOE 1-)[4,36,37].

Early colostrum administration, usually within the first 48 postnatal hours, is done either by repeated instillation inside the cheeks using oral syringe or gentle application over the tongue, around the gums, and along the lips using a swab or sponge soaked with 0.1 to 0.5 mL of colostrum, or by oropharyngeal administration of mother's own fresh or frozen/thawed colostrum, irrespective of when enteral feeding is initiated[36].

In brief, oral or oropharyngeal administration of mother's own colostrum administered within the first 48 postnatal hours is safe and may be beneficial to very preterm infants[4]. However, there are no current data to support the recommendation of routine use of this procedure[4].

Nasogastric versus orogastric tube feeding

Nasogastric tubes increase nasal airway resistance and may lead to higher total airway resistance, while orogastric tubes may provoke vagal stimulation and bradycardia due to tube movements in the hypo-pharynx[4].

No evidence exists to prefer using either nasogastric or orogastric feeding tubes (LOE 2), so local preferences are allowed[4].

Starting volume of feeds

In a recent national multi-center cohort study in very preterm infants[38], investigating the optimal time point after

birth at which enteral nutrition could be started, it was concluded that enteral feeding should be initiated preferably within 24 postnatal hours since it may promote feeding tolerance, shorten the time to reach total enteral feeding, and reduce the incidence of growth restriction and late-onset sepsis, without increasing the risk of NEC (LOE 3).

Studies conducted more than 20 years ago in very preterm infants have reported advantages on initiating feeding using 'minimal enteral feeding' (MEF) or 'trophic feeding', defined as nutritional insignificant small volumes of feeds (typically 12-24 ml/kg/day) without advancement for 3-7 days (LOE 1+)[4]. However, there is no current evidence of a beneficial effect of maintaining for any period the MEF volume intake compared to advancing feeds immediately after birth (LOE 1+)[4].

It is recommended that in most preterm infants, enteral feeding should be initiated within the first 24 postnatal hours, with 12-24 ml/kg/day, preferably using MOM or DHM, and advanced as soon as the infant tolerates it (GOR B)[4,38].

Advancing volume of feeds

After 4 postnatal days, feeding advancement of 30 mL/kg/day does not significantly increase the incidence of NEC or mortality compared to slower 15-20 mL/kg/day advancement that was formerly used (LOE 1+)[4,39,40].

It is recommended that in stable preterm infants, feeding should be advanced by 18-30 mL/kg/day, especially if MOM is used (GOR A)[4,20].

Bolus versus continuous feeding

Bolus feeding, promoting the cyclical release of gastrointestinal tract hormones that stimulate gut maturation and motility, is assumed to be is more physiological[4]. However, it should be kept in mind that bolus feeding, in comparison with continuous feeding, may increase splanchnic perfusion and energy expenditure, potentially compromising growth[4,41].

A meta-analysis of randomized controlled trials comparing continuous feeding with intermittent bolus feeding in VLBW infants did not find significant differences in feeding intolerance, duration of parenteral nutrition, growth, necrotizing enterocolitis, and duration of hospitalization[42]. Nevertheless, using continuous feeding, the time to achieving full feeds was longer (LOE 2+)[4,42]. On the other hand, continuous feeding has the inconvenience of greater fat adherence to the inner wall of the tube compared to bolus feeding[43] with risk of losing energy and fat content[4].

In VLBW infants, systematic reviews and meta-analyses concluded that while using intermittent feeding, 3-hourly versus 2-hourly feeding intervals are comparable, although extremely low-birth-weight (ELBW) infants (birth weight < 1000 g) may reach full enteral feeds earlier when fed twice-hourly[44,45].

In brief, in VLBW infants, continuous and intermittent bolus feeding seem comparable, as are comparable 3-hourly or 2-hourly feeding intervals in intermittent feeding (LOE 3)[4,20]. In infants < 1000 g, a 2-hourly interval may be preferable (LOE 3)[44,45].

Pacifier use

The Baby-Friendly Hospitals Initiative considers that, in preterm infants, pacifiers are appropriate during tube feeding, and nipple shields can be used to facilitate establishment of breastfeeding, under qualified support and attempts at the breast[5]. Non-nutritive sucking using a pacifier during tube feeding was reported to mature and maintain the sucking reflex, improve digestion, provide comfort, and promote neurobehavioral organization (LOE 3)[4,46]. Additionally, systematic reviews concluded that pacifier use in preterm infants helps transition from tube to oral feeding, breastfeeding, faster weight gain, and earlier discharge from the neonatal unit, although the relationship between pacifiers and breastfeeding is more complicated as it appears to be influenced by additional risk factors (LOE 3, GOR C)[47,48].

In brief, non-nutritive sucking using a pacifier, during tube feeding, may have benefits (LOE 3)[4].

Oral feeding

Infant oral feeding performance is the result of the infant skills to coordinate sucking, swallowing, breathing, and esophageal transport of feeds[4].

In relation to bottle feeding, cup feeding seems to be a good alternative as avoidance of bottle feeding may increase breastfeeding, not only at discharge but also up to six months post discharge (LOE 2-)[49].

The finger-feeding method may be effective for increasing sucking abilities and accelerating transition to breastfeeding (LOE 2)[50,51]. According to this method, the tip of a feeding tube is cut and fixed with adhesive tape to the inner side of the gloved small finger of the caregiver. The other end of the tube is connected to a syringe without the plunger, containing MOM or DHM. The milk slides through the tube as the sucking pattern is adjusted by the infant and not by gravity, at which point the pulp of the small finger faces the hard palate and the infant will begin sucking[50,51].

Establishing oral feeding may be more challenging in infants with BPD in whom micro-aspirations may compromise respiratory capacity further[4].

In brief, oral feeding should be initiated from 32 weeks PMA, provided stability and competences of the infant are considered (GPP)[4].

Human milk fortification

Although under certain circumstances very few preterm infants may receive the required nutrient intake from native breast milk alone[15,20], in the majority the nutritional content of HM should be adapted to the high requirements for their growth[4]. In this regard, supplementation of HM with multi-nutrient fortifiers may prevent nutritional deficits, while taking advantage of HM biological properties (LOE 2+)[4].

While fortifying HM, it should be kept in mind that energy and macronutrient content may vary greatly either in MOM, according to the lactation time[18], or in DHM, depending on being single or multiple pools[52]. DHM may require higher levels of fortification than MOM (LOE 2+)[4].

Bovine-based multi-nutrient fortifiers are commonly used, but more recently HM-based multi-nutrient fortifiers were developed. The HM-based fortifiers may reduce the risk of NEC compared with bovine-based fortifiers, but there are insufficient reliable data to determine the optimal strategy (LOE 2+)[4].

Addition of multi-nutrient fortifier to HM increases the osmolality of feeds, 70% occurring just after the fortifier addition and a further rise due to hydrolysis of carbohydrates by amylase activity of HM[53,54]. To avoid this additional increase in osmolality, the addition of the fortifier just before feeding has been proposed (GPP)[55], although this strategy may be laborious and time consuming.

In some neonatal units, half-strength fortification (or even lower strength) is used at the beginning and subsequently increased to full-strength fortification according to infant's tolerance, despite no strong evidence existing to support this practice[7,55,56].

To summarize, fortification of HM using multi-nutrient fortifier is recommended (GOR A) in preterm infants[4], particularly in those born at < 32 weeks[20] or even in those weighing < 1800 g[7].

When to start fortification

The optimal time to start fortification is not determined yet. Nevertheless, early fortification seems to be as safe as delayed fortification, reducing cumulative nutrient deficiencies and being beneficial for the bone metabolism (LOE 2+)[4].

Initiation of HM fortification is recommended when HM intake reaches 40-100 mL/kg/d (GOR C)[4].

Methods of fortification

Standard fortification

The standard fortification, using powder or liquid multi-nutrient fortifiers for HM, is the commonest method currently used in most of the neonatal units[57]. In standard fortification, a fixed amount of fortifier is added to HM, according to the manufacturer's recommendations[7].

This method overlooks the great variability of the nutritional composition of HM, increasing the risks of energy-protein malnutrition, which include extrauterine growth restriction, poor neurodevelopment, and metabolic bone disease[7].

Addition of a multi-nutrient fortifier to HM is recommended to support growth in preterm infants (GOR A). In standard fortification, the fixed amount of fortifier indicated by the manufacturer should be added to HM.

Individualized fortification

In individualized fortification, to compensate for the variation in macronutrient content of HM, not accounted in standard fortification, modular macronutrient supplements are added to fortified HM. These modular supplements include hydrolyzed protein, fat in the form of medium-chain triglycerides, and carbohydrate in the form of glucose polymers[7,58]. It should be kept in mind that addition to fortified HM of extra protein and glucose polymers increases the HM osmolarity[59,60]. Thawing increases osmolarity after fortification when compared with fresh milk[60].

Two alternative methods of individualized fortification are proposed: adjustable fortification and target fortification[7].

Adjustable fortification. The protein content of some HM multi-component fortifiers may be insufficient to increase protein concentrations in HM to recommended intake levels (LOE 2)[4]. Using the adjusted fortification, protein intake is adjusted to the infant's metabolic response, using blood urea nitrogen (BUN) as a surrogate for protein adequacy. To be adequate, serum BUN levels should vary between 10-16 mg/dL (blood urea 21.40-34.24 mg/dL)[7]. The adjustable fortification method usually is initiated with standard fortification, and as soon as full-strength fortification is tolerated, BUN is regularly assessed. BUN levels < 10 mg/dL indicate that extra protein should be added in the form of modular

protein, and BUN levels > 16 mg/dL indicate that the amount of fortification should be reduced[7].

Target fortification. Using this method, regular measurements of energy and macronutrient content of HM is performed, guiding the possible addition of modular supplements of protein, fat, and carbohydrates to fortified HM to reach the desirable nutrient targets in each infant[7,58,61]. This method has the inconvenience of requiring an expensive HM analyzer and being time-consuming and labor-intensive[7].

To summarize, individualized fortification may be adequate in alternative to standard fortification (GOR A)[4]. In adjustable fortification, standard fortification is started, and extra modular protein is added to fortified HM if BUN is <10 mg/dL[7]. In targeted fortification, modular protein, medium-chain triglycerides, and/or glucose polymers are added to fortified MOM, guided by HM macronutrient content measurements, to reach the desirable nutrient targets[7,58].

Gastric residuals

Gastric residuals (GR) are commonly used to define feeding tolerance. The type of enteral feed and positioning of the infant have an impact on gastric emptying. Gastric emptying is almost twice as fast with breastmilk than with formula[4]. On the other hand, the prone position in the first half hour after feeding may promote a faster gastric emptying (LOE 2+)[4].

Criteria based on volume percentage of the previously administered feed, checked in gastric aspirates, were previously used to consider a GR as significant[4,62]. However, no data regarding the volume and/or color of GR are sufficiently reliable to indicate feeding intolerance or to predict NEC[4].

Routine monitoring of GR is reported to increase the risk of feed interruption episodes and time to reach full enteral feeds and does not have an impact on NEC incidence (LOE 2+)[63].

There is no consensus on whether to re-feed or discard the gastric aspirate[4].

In brief, routine monitoring of GR is not recommended in clinically stable infants (GOR B)[4]. Gastric residuals should be otherwise assessed when clinical signs of NEC are present, such as extreme abdominal distension, tenderness, emesis, bloody stools, apnea, and temperature instability (GOR B)[4].

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Conflicts of interest

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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