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GUIDELINES

Guidelines for enteral nutrition in infants born preterm: 2023 update by the Portuguese Neonatal Society. Part II. Enteral feeding in specific clinical conditions and feeding after discharge

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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 into two parts. Part I addresses the nutrient requirements and the enteral feeding approach during the hospital stay, including optimization of 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. Mother's own milk. Nutrient requirements. Preterm infants.

Recomendações para a nutrição entérica na criança nascida pré-termo: atualização em 2023 da Sociedade Portuguesa de Neonatologia. Parte II. Particularidades da nutrição entérica em situações clínicas especiais e na alimentação após a alta

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

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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 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: Fórmula láctea. Fortificação do leite humano. Leite materno. Necessidades nutricionais. Nutrição entérica. Recém-nascido pré-termo.

Feeding in specific clinical conditions

Intrauterine growth restriction

Infants with intrauterine growth restriction (IUGR) may have impaired gut function because of reduction of gut perfusion, resulting in higher risk of feeding intolerance, gut perforation, and NEC[1].

Bell's modified criteria were developed specifically for severity staging of NEC, although this entity seems to include more than one disease with different pathophysiological etiologies and clinical presentations[2]. When prenatal hypoxic-ischemic event is the dominant pathophysiological factor, intestinal injury and inflammation begin in-utero and become clinically apparent in the first postnatal week. Preterm infants who develop NEC before 7 postnatal days were reported to have higher incidence of fetal umbilical artery Doppler velocimetry abnormalities, IUGR, delayed passage of first meconium, and higher levels of inflammatory markers in the first postnatal hour compared with those who developed NEC later[2].

In IUGR, the degree of prematurity is a major risk factor for feeding intolerance and NEC and a concern when deciding to introduce enteral feeding[3]. In a systematic review of 14 trials including 1551 very preterm infants with IUGR, it was concluded that delaying the introduction of progressive enteral feeds beyond four days after birth (compared with earlier introduction) may not reduce the risk of NEC; conversely, delayed introduction may slightly reduce feed intolerance whereas it may increase the risk of invasive infection[4]. Different results may be found in more immature infants. In a randomized clinical trial of IUGR infants born < 29 weeks after gestation, with abnormal antenatal Doppler measurements, they failed to tolerate enteral feedings compared with more mature infants, and it was suggested that a slower advancement of feeds is required in these cases[5].

A retrospective study in a Portuguese level III neonatal intensive care unit determined, in infants with abnormal antenatal Doppler flow patterns, the effect time of first enteral feeding on the incidence of gastrointestinal morbidity; 86.7% of infants were small for gestational age and 64.3% were VLBW infants[6]. It was found that early feeding introduction (≤ 48 postnatal hours), compared with late feeding introduction (> 48 postnatal hours), appeared not to increase feeding intolerance and NEC, while seaming to be a significant adjusted protective factor for late-onset sepsis[6].

To summarize, in very preterm infants with IUGR, delaying the introduction of progressive enteral feeds beyond four postnatal days seems not to be advantageous (LOE 1+)[4]. Slow advancement of feeds should otherwise be considered when introducing enteral feeding in infants with IUGR < 29 weeks' gestation (LOE 1+)[5].

Umbilical artery catheter

In a prospective study it was found that insertion and removal of umbilical artery catheters and aspiration of blood and bolus infusion of fluids into these catheters do not diminish the blood flow velocity or increase the vascular resistance in the superior mesenteric artery, especially when minimal enteral feeding is used[7].

Therefore, it seems not to be necessary to change the enteric nutrition approach in infants with umbilical artery catheter, particularly in those receiving minimal enteral feeding (LOE 3)[7].

Patent ductus arteriosus

The management of enteral feeding in preterm neonates with hemodynamically significant patent ductus arteriosus (hs-PDA) continues to be a matter of debate[8]. In preterm infants, the lack of robust evidence in support of or against a timely introduction of feeding or withholding feeding in the presence of hs-PDA and during pharmacological PDA closure does not allow drawing any related recommendation[8]. While waiting

for further data, the feeding management of this population should be individualized, based on the infants' hemodynamic and clinical characteristics[8].

In a prospective study of ELBW infants with PDA without pharmacological treatment, it was concluded that large PDA (PDA/left pulmonary artery ratio ≥ 1) was associated with attenuated intestinal blood flow responses to feedings, later achievement of full enteral intake, and higher rates of NEC than in small and moderate PDA[9].

In infants born after > 26 weeks of gestation, minimal enteral feeding (20-40 mL/kg/day) by 48-96 postnatal hours, with concomitant use of a standard oral ibuprofen schedule (10 mg/kg/dose and 5 mg/kg/dose every 24 h, a 3-day course) was associated with higher ductal closure rates without increased gastrointestinal morbidity[10].

To summarize, feeding withholding may be considered in preterm infants with large hs-PDA (LOE 3)[8,9]. Limited evidence suggests that minimal enteral feeding may be used while treating PDA with oral ibuprofen (LOE 4)[10,11].

Packed red blood cell transfusion

In a recent retrospective case-control study of VLBW infants, the higher number of packed red blood cell (PRBC) transfusions and total volume of transfusions were associated with increased odds for NEC[12]. The pathophysiology of this association seems to be immunological, possibly through alterations of mesenteric arterial reactivity and nitric oxide pathways[13].

Three meta-analyses of observational studies assessed the association between PRBC transfusions and NEC modified Bell's stage IIa or greater. A meta-analysis found that recent exposure to transfusion was associated with NEC, but some studies did not adjust for confounders[14]. On the contrary, a meta-analysis of low-to-moderate quality studies could not demonstrate a significant association between transfusions and NEC[15]. In another meta-analysis, a protective effect of recent (within 48 h) transfusion on the subsequent development of NEC was even found[16].

Only one study was elected in a systematic review of randomized controlled trials, in which evidence was insufficient to determine whether withholding feeds around the time of PRBC transfusion influenced the incidence of subsequent NEC[17].

In brief, while waiting for robust evidence, a personalized feeding approach should be adopted in infants undergoing PRBC transfusions, according to the infants' hemodynamic and clinical characteristics (LOE 4)[18].

Refeeding after necrotizing enterocolitis

A systematic review and meta-analysis of observational retrospective studies assessed the effects of earlier (5-7 days) vs. later (median 10 days) re-initiation of enteral feeds after non-surgical NEC diagnosis[19]. Earlier re-initiation of enteral feeds resulted in significantly lower risk for recurrent NEC and/or post-NEC stricture[19].

In infants with NEC Bell's modified stage II, a consensus-based standardization of time to re-initiate feeding resulted in shortening the time to reach full enteral feeds (9.4 to 5.1 days) and central line days. In this protocol, feeding was withheld until normalization of abdominal exams after removal of gastric tube, and trophic feeds were re-initiated using MOM or DHM for at least three days[19].

In brief, after a non-surgical NEC diagnosis, it is preferable to re-initiate enteral feeds before 7 days after diagnosis (LOE 1)[19]. Standardization of time to re-initiate enteral feeding, using HM, may shorten the time to reach full enteral feeds and central line days (LOE 3)[19].

Bronchopulmonary dysplasia

In preterm infants, the development of BPD has been associated with postnatal deficit of energy and nutrients and growth restriction[20-22].

A meta-analysis of randomized controlled studies, determining the effect of fluid intake on morbidity and mortality in premature infants, concluded that fluid restriction was associated with a trend towards a reduced risk of BPD[23]. In these cases, a reasonable approach is not to exceed 135-140 mL/kg/day[24]. In fact, a fluid intake of 135 mL/kg/day is considered the minimum enteral volume to supply sufficient energy and nutrients in healthy preterm infants[25]. On the other hand, this may be the maximum fluid intake tolerated by infants with severe BPD[23].

Concerning nutrient intake, it is advisable that infants with confirmed BPD receive an energy intake of 120-150 kcal/kg/day and protein intake of at least 3.5 g/kg/day[24,26]. Providing such high-energy intake in low volumes of feeds remains a challenge and requires concentrating energy and macronutrients in administered feeds[20]. Target HM fortification was reported to result in improved weight gain velocity in infants with BPD[26]. When HM is insufficient or unavailable, preterm formulae containing high energy and protein densities are an alternative in fluid-restricted infants with BPD[27]. A further increase in energy intake, using modular digestible sources, may be preferable to concentrating

formulae beyond the manufacturer's recommendations[24]. When compromised pulmonary function requires extreme fluid restriction, addition of medium-chain triglyceride and glucose polymers to preterm formulae can be a strategy for providing higher energy intake in low volumes of feeds[28]. However, such formulae manipulation has risks inherent to increasing the osmolality of feeds and compromising the optimal energy-to-protein ratio[29].

Tube feeding for a long period of time may be required in preterm infants with BPD (Rocha 2021). In addition, the prevalence of gastroesophageal reflux is high in BPD infants, particularly acid reflux in ELBW infants[30].

To summarize, in infants with confirmed BPD, the suggested intakes are: fluid 135-140 mL/kg/day, energy 120-150 kcal/kg/day, and protein at least 3.5 g/kg/day (LOE 3)[24,26].

Feeding after discharge

Preterm infants tend to be discharged from the hospital earlier than the expected term, therefore they may be sleepier and have more difficulties in latching, sucking, milk transfer, and swallowing than full-term infants[31]. Moreover, the preterm population is quite heterogeneous depending on the degree of prematurity and persistent morbidities such as BPD[31].

The last ESPGHAN commentary on feeding preterm infants after hospital discharge was published in 2006[32]. Since then, new research on this topic has been published and some aspects addressed in this position paper need to be updated (Table 1).

Breastfeeding

Two independent cohort studies on preterm infants found an association between exclusive breastfeeding (without MOM fortification) after discharge and improved cognitive outcomes, despite being associated with an initial suboptimal weight gain[33].

Fortifying MOM at home may be problematic due to the fear that fortification can disrupt the routine of breastfeeding[34,35]. Consequently, MOM fortification is often discontinued with the subsequent risk of nutritional deficits and suboptimal weight gain during the first weeks after discharge[34]. Nevertheless, other authors have described that fortification after discharge is well accepted by parents, without an increase in reported adverse events[36].

On the other hand, many studies have reported the clinical advantages of fortifying MOM up to 4-6 months of corrected age, including better weight, length, head growth, bone mineral density, lung function, and visual function[31,34,37]. Accordingly, the European Milk Bank Association Working Group on Human Milk Fortification suggests considering MOM fortification after discharge in breastfed preterm infants who failed to grow adequately before fortification of HM[38].

Cessation of MOM fortification after discharge is not consensual. Some suggest stopping fortification at around 6 to 12 weeks post term age, while others suggest discontinuing only once infants have achieved some catch-up growth[39].

A method similar to the one used in a large cohort study of preterm infants can be followed: every day, 3.55 g of HM multi-nutrient fortifier is added to 50 mL of fresh or defrosted MOM and offered by bottle feeding, once a day, up to 4-6 months of corrected age[40].

To summarize, preterm infants discharged with satisfactory growth can maintain exclusive breastfeeding under close growth monitoring. MOM fortification is advisable in infants fed non-fortified HM discharged with unsatisfactory growth, or if weight gain becomes suboptimal after discharge (LOE 4)[32,38]. In these cases, fortification can be discontinued at 6-12 weeks post term age (LOE 4)[39].

Formula feeding

When breastfeeding is not possible or is insufficient after hospital discharge, ESPGHAN[32] suggests that infants with satisfactory growth should be fed term infant formula enriched with long-chain polyunsaturated fatty acids[32]. Infants with suboptimal growth should be fed fortified post-discharge formula[32].

In a meta-analysis of 16 eligible trials with a total of 1251 preterm infants evaluated after discharge, the effects on growth and neurodevelopmental outcomes of using post-discharge formulae (74 kcal/100 ml) and preterm formulae (80 kcal/100 ml), in comparison to standard term formulae (67 kcal/100 ml), and concluded that there is no evidence to support a recommendation to use post-discharge formulae[41]. No consistent evidence was found of the benefit of post-discharge formulae on growth up to 12 to 18 months post term[41]. Limited evidence suggests that feeding preterm formula (which is generally available only for in-hospital use) may increase growth rates up to 18 months post term[41]. Although no advantages were found in this meta-analysis of using post-discharge formulae, a positive association between weight gain in the first 3-4 months after term age and later cognition has been reported[42,43].

Table 1. Feeding after discharge approach, including breastfeeding, formula feeding, and complementary feeding[35]

Procedure	Observations	LOE
Breastfeeding	If satisfactory growth: continue exclusive breastfeeding and growth monitoring. If suboptimal growth: fortify mother's own milk.	4
Formula feeding	When MOM is not available or is insufficient. If satisfactory growth: use a term infant formula supplemented with LCPUFAs. A post-discharge formula can be used, up to 3-4 months CA, to optimize early brain development. If suboptimal growth: use a post-discharge formula.	4
Complementary feeding	Introduce complementary feeding at 5-8 months chronological age, provided 3 months CA and adequate developmental skills were reached. Introduce potentially allergenic foods and gluten when complementary feeding is started.	4
Iron	In very preterm infants: iron intake of 2-3 mg/kg/day up to 6-12 months CA, either as iron supplements or through iron-fortified formula (if breastfeeding is insufficient). In late preterm infants born with 2000-2500 g: iron supplements of 1-2 mg/kg/day, from 2-6 weeks to 6 months chronological age. From 6 months chronological age: offer iron-rich complementary foods (eg, meat and fish) and iron-fortified cereals.	4

Levels of evidence (LOE) in descending order: 1 to 4[49].
CA: corrected age; LCPUFAs: long-chain polyunsaturated fatty acids.

To summarize, when MOM is not available or is insufficient after discharge, infants should be fed formula[32]. Infants with satisfactory growth can be fed term infant formula enriched with long-chain polyunsaturated fatty acids[32,35]. Infants with suboptimal growth can be fed post-discharge formula (LOE 4)[32,35]. Otherwise, post-discharge formula can be used in preterm infants with satisfactory growth up to 3-4 months after term age, as a strategy to optimize early brain development (LOE 4)[31].

Complementary feeding

Guidelines on the optimal time for starting complementary feeding in preterm infants and the ideal composition of feeds are missing[31,44]. Preterm infants are commonly weaned earlier (before 4 months of chronological age) than their term counterparts[35].

Multiple and unpleasant procedures experienced by preterm infants during hospital admission, such as orogastric/nasogastric tube feeding, suctioning, and intubation, may lead to a negative attitude when introducing complementary feeding[35]. Defensive behaviors found in preterm infants include refusal to open the mouth, food selectivity, and feeding rejection[45].

Adequate neurodevelopmental skills that include control of the neck, disappearance of tongue protrusion reflex, reduction of reflexive suck in favor of lateral tongue movements, and the gradual appearance of lip seal, are critical when deciding to start complementary feeding[35].

A systematic review of infants born preterm suggests starting complementary feeding at 5-8 months of chronological age, provided infants have reached 3 months of corrected term age and they have acquired the necessary neurodevelopmental skills[46].

The timing to start complementary feeding in preterm infants does not seem to influence the incidence of later overweight and obesity[35].

In a multicenter cohort study, it was found that very early introduction of complementary foods (including egg, fish, and tomato) into the diet of preterm infants did not increase the incidence of food allergies or atopic dermatitis, even among the most preterm infants, suggesting that their gut-associated lymphoid tissue is ready for complementary foods within 3-6 months of chronological age, regardless of gestational age at birth[47]. A recent systematic review evaluating the timing to introduce potentially allergenic foods and gluten concluded that allergenic foods may be introduced when complementary feeding is started, any time after 4 months of corrected term age, and large amounts of gluten should be avoided during the first few weeks after its introduction, despite limited evidence supporting this recommendation[35,47,48].

In infants with oral dysfunctions or comorbidities, an individualized multidisciplinary intervention is required, encompassing nutritionist, speech therapist, and behavioral psychologist[31,35].

In brief, in infants born preterm with adequate developmental skills for corrected term age, complementary feeding can be introduced at 5-8 months of

chronological age, provided they have reached 3 months of corrected term age (LOE 4)[35,46]. Potentially allergenic foods and gluten can be introduced when complementary feeding is started (LOE 4)[35,48].

Iron

In infants born preterm, iron supply is a matter of concern due to its essential role for brain development[35].

In very preterm infants, 2-3 mg/kg/day of iron is recommended up to 6-12 months of corrected term age, either as iron supplements or through iron-fortified formula if breastfeeding is insufficient (GOR GPP)[49].

Late preterm infants born with 2000-2500 g, should receive iron supplements of 1-2 mg/kg/day, from 2-6 weeks to 6 months of chronological age[50].

From the age of 6 months, iron-rich complementary foods should be preferred, including meat, fish, and iron-fortified cereals (LOE 4)[35,50].

Conclusions

These updated Portuguese Neonatal Society guidelines are mainly oriented by similar 2022 updated recommendations by ESPGHAN and WHO.

In stable preterm infants, enteral feeding should be initiated within the first 24 postnatal hours, with 12-24 mL/kg/day. Subsequently, feeding advancements should be of 18-30 mL/kg/day.

Fresh MOM is the first choice and institution-based multidisciplinary interventions are crucial to promote HM feeding. When MOM is not available, DHM is the second choice if available. At least in very preterm infants, HM should be supplemented with multi-nutrient fortifier, and if necessary, modular macronutrient supplements should be added to fortified HM. Preterm formula is the best alternative when HM is not available.

Feeding preterm infants should be adapted in certain clinical conditions, although there is still no robust evidence available to support clinical protocols for these specific cases.

Some recent data on how to feed preterm infants after discharge, including MOM fortification and initiation of complementary feeding, have been available, although the level of evidence is still low.

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Conflicts of interest

None.

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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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