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Implementing guidelines for enteral nutrition of preterm neonates during intensive care and in later infancy

Implementando diretrizes para nutrição enteral de neonatos prematuros durante a terapia intensiva e na infância posterior

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Providing critically ill neonates with adequate nutrient intake is often impossible. This is due to the constraints on fluid intake, metabolic imbalances, inability to utilize the enteral route due to intestinal dysmotility, and risk of complications such as necrotizing enterocolitis. Consequently, postnatal or extrauterine growth restriction (EUGR) occurs frequently, manifesting as weight loss beyond that caused by the normal extracellular volume contraction which must occur during the transition from fetal to extrauterine life. While it is impossible to partition the direct effects of nutritional deficits versus confounding variables associated with preterm birth, mitigating nutritional deficiencies likely plays a role in improving outcomes related to morbidities such as EUGR, anemia, osteopenia of prematurity, retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis, and neurodevelopmental deficits[1-3].

The potential for nutritional management to affect postnatal growth and subsequent outcomes can be discerned from observational studies of variation in postnatal growth rates and in the resulting incidence of EUGR at NICU discharge across Europe. When defining EUGR as discharge weight < 10th percentile, the incidence of EUGR was highest in Portugal, ranging between 43% (using Intergrowth charts as a reference) and 60% (based on Fenton charts)[2]. Adjusting for differences in average birth weight at term and other country-specific confounders diminished the observed variation to a minor degree, leaving substantial unexplained variation in postnatal growth between countries. These variations present an opportunity for research and collaborative clinical quality improvement (QI) efforts to optimize postnatal nutrition.

Whether relying on QI or research approaches, it is essential to develop and implement standardized interventions. Protocolizing feeding processes not only enables effective implementation, but it also improves growth[4] and decreases the risk of necrotizing enterocolitis[1]. The Portuguese guidelines for enteral nutrition in preterm neonates reported in this issue[5,6] are a fundamental element to enable such improvement. Used in conjunction with the previously published guidelines for parenteral nutrition[7,8], and standardized postnatal growth monitoring[9,10], these recommendations should allow for improved nutritional status during the acute stage of postnatal transition, as well as the convalescent stages preceding discharge from NICU. The guidelines underscore the importance of mother's own milk (MOM) as the optimal base for infant feeding, including preterm infants. However, MOM is frequently inadequate to meet the nutritional needs of the preterm neonate. Additionally, preterm birth presents unique challenges and subsequent decreased provision of MOM[11]. A framework for

establishing NICU systems which promote and optimize the provision of MOM, with close nutritional monitoring and individualized supplementation that takes into account the infant's body composition, acute versus convalescent disease states[12], and MOM supply over time is essential to optimize enteral nutrition in preterm neonates. The complexity of nutritional optimization under these conditions benefits from the expertise and dedicated time availability of a dietitian.

Whereas dedicated dietitians who integrate the neonatal nutrition care team help optimize feeding in the NICU, their nutritional assessments and plans are foundational for post-discharge feeding of preterm infants that attempts to correct and prevent nutritional deficits. Post-discharge feeding is addressed separately in Part II of the recommendations[6], a strategically wise choice which makes these guidelines more likely to be used by pediatricians practicing in the community. Nutritional management in a decentralized outpatient setting is much more difficult to standardize than during NICU care. Consequently, post-discharge nutrition and growth of preterm neonates have received limited research and QI efforts.

Maximizing adoption of these nutritional guidelines is essential to optimize population health outcomes. In inpatient settings, implementation of the guidelines can be further enabled by integration into electronic records or prescribing systems, automated calculation of nutritional intakes and development of a nutritional monitoring dashboard to facilitate the task of neonatal dietitians -where available- or of neonatologists or other neonatal care providers. In the ambulatory setting, it is unlikely that practicing pediatricians will immediately learn and adopt the new guidelines through continuing education, and uniformly change their established practices. Absent neonatal dietitians, clarity and simplicity are important features underlying the usability of the guidelines by pediatricians. To this end, simplified guidelines, reminders, and possibly tools that can be integrated into electronic health record systems are needed to facilitate guideline use and achieve buy-in from practicing pediatricians.

The family is an essential element of the infant's nutritional support team, not only in committing to providing mother's milk, but also in helping to bridge the transition from inpatient care of the preterm "feeder and grower" to the still-evolving ambulatory feeding strategies. Informed parents can advocate for continuity of nutritional plans set in NICU in preparation for discharge, and they may be capable of asking "the right questions" when pediatricians make recommendations for routine infant feeding practices which may not be based on current evidence. To that end, it would be useful to have family educational tools that highlight key nutritional guidelines in lay persons' language, and which can be used by dietitians or other providers of a customized nutritional prescription plan in preparation for discharge. Using such a tool to communicate the nutritional plan to the pediatrician can reinforce continued use of the guidelines during infancy.

The combination of parenteral and enteral nutritional guidelines during NICU care, simple post-discharge recommendations, and systems for effective implementation of these guidelines, which utilize the family to help ensure continuity across care settings, has the potential to minimize the incidence, severity, and consequences of postnatal micronutrient deficiency and/or malnutrition, growth restriction and their consequences in neonates born preterm.

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Parents, children, and pacifiers in Portugal: use, beliefs, and evidence, a cross-sectional study

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Abstract

Objective: To determine the prevalence of pacifier use in Portugal and its association with otitis media infections, speech sound disorders, dental problems, gastroenteritis, and breastfeeding difficulties and analyze parents' knowledge and beliefs regarding pacifier use. **Methods:** Observational study using an online questionnaire destined to all parents' resident in Portugal, enquiring parents' perceptions regarding pacifier use and child health problems and language development. **Results:** Pacifier use was positively associated with increased risk of middle ear infections and sleep problems but not language development problems, gastroenteritis episodes, dental problems, or breastfeeding difficulties. **Conclusion:** This study outlines the importance of informing parents about the pros and cons of pacifier use supporting individualized and informed decision.

Keywords: Children. Parents. Pacifier. Portugal.

Pais, filhos e chupetas em Portugal: uso, crenças e evidências, um estudo transversal

Resumo

Objetivo: Determinar a prevalência do uso de chupeta em Portugal e a sua associação com otite média aguda, gastroenterite aguda, alterações da fala, problemas dentários e dificuldade na amamentação; avaliar as ideias dos pais em relação à utilização de chupetas nas crianças. **Métodos:** Estudo observacional baseado na aplicação de um questionário online dirigido a pais residentes em Portugal, com questões relativas à perceção dos pais quanto ao uso da chupeta e problemas de saúde e de desenvolvimento da fala das crianças. **Resultados:** O uso de chupetas foi associado positivamente ao aumento do risco de otite média aguda e alterações do sono, mas não com episódios de gastroenterite aguda, alterações do desenvolvimento da fala, problemas dentários ou dificuldade na amamentação. **Conclusão:** Este estudo realça a importância de informar os pais relativamente às vantagens e desvantagens da utilização de chupeta, para que possam tomar uma decisão individualizada e informada.

Palavras-chave: Crianças. Pais. Chupeta. Portugal.

Keypoints

What is known
– Pacifier's use is very common in western countries.
– The use of pacifiers can be associated with middle-ear infections and dental problems.
– The use pacifiers in older children should be discouraged, as it has no benefits.

What is added
– This study reinforces the need to inform parents about pacifiers, as a significant percentage doesn't seek information about it.
– There was an association between the use of pacifiers and sleep abnormalities.

Introduction

Non-nutritive sucking with pacifiers in various forms has been used by humans for possibly thousands of years[1]. Non-nutritive sucking (NNS) is a natural reflex present in fetuses and newborns that helps with nutrition[1], manifested by sucking hands and fingers[2]. The use of pacifiers is very common, about 75-80% of babies in occidental countries[2], but its benefits and costs remain surrounded with controversy.

On the one hand, parents believe that the pacifier helps soothe the crying or fussy baby, putting the baby to sleep, weaning, avoiding finger sucking; also, evidence suggests that pacifier use helps calming pain and prevents sudden infant death syndrome (SIDS)[3].

On the other hand, exclusive breastfeeding, nipple confusion, otitis media infection, breathing, orofacial development, dentition, dental occlusion, mastication, and speech sounds articulation remain as sources of concern for many parents and professionals[2].

The present paper aims to determine the prevalence of pacifier use in Portugal and characterize it; to determine the existence of otitis media infections, speech sound disorders, dental problems, gastroenteritis, and breastfeeding difficulties and compare it between users and non-users. Moreover, it intends to measure the parents' knowledge about the advantages and disadvantages of pacifier use, comparing it with the most recent evidence about clinical recommendations on this matter.

Methods

We conducted an observational, descriptive, transverse study, based on an online questionnaire given to all parents living in Portugal, in Portuguese. This anonymous questionnaire was made available during one month as a *Google® Form*, promoted in parents' groups, through different digital platforms, like social media networks, instant message, and email providers. It contained 40 open and closed questions, versing child and parents' social and demographic information, parents' ideas and opinions about pacifier use (advantages and disadvantages, prevention of health problems, information sources) and data concerning child pacifier use (age of onset, type of pacifier used, intensity of use, situations and motives for use, addition of substances, age of pacifier withdrawal and difficulties in the process), food and sleep habits, child health problems (physical growth, middle ear infection, gastroenteritis and dental problems) and language development (language difficulties and/or speech therapy intervention, age at first word, considered a problem after 18 months).

We asked each family for a single answer – individual as a couple – and, in case of more than one child, answers should report to the youngest.

Data record and statistical analysis was made in *Microsoft Excel®* 2010 and *SPSS®* version 24. We conducted a descriptive analysis with absolute and relative frequencies for categorical variables and with averages and standard deviations for continuous variables. Two groups, those who use and those who do not use pacifiers, were compared. For group analysis we used the *Chi-Square test* for statistical relations between dependent binary variables and independent binary variables, and *t-Student test* for non-categorical variables. *P-values* < 0.05 were considered statistically significant.

Informed consent was provided with the questionnaire and obtained through parents answering the questionnaire. The study protocol was submitted and approved by Administração Regional de Saúde de Lisboa e Vale do Tejo ethical commission.

Results

From the 531 submitted questionnaires, 519 were validated and 12 were eliminated due to inconsistencies. Families from all regions of Portugal submitted the questionnaire, with a major representation of Lisboa (36,4%), Coimbra (14.1%) and Porto (11.8%). Both, parents and children's sociodemographic variables are characterized in Table 1. The sample had mostly only-child families and the most represented children age groups were 0-6 months old (22.4%), 12-24 months old (25%) and 2-3 years old (31.4%) and sex distribution was similar. Most parents were aged between 30-39 years old and had higher education.

Table 1. Sociodemographic characteristics (n = 519)

	Users (n = 403)	Non-users (n = 116)	Total n (%)
Family characterization			
Informant			
Mother	390 (97%)	110 (95%)	500 (96.3%)
Father	13 (3%)	6 (5%)	19 (3.7%)
Health professional	118 (29%)	20 (17%)	138 (26.6%)
Mother			
Age			
20-29 years old	71 (18%)	20 (17%)	91 (17.5%)
30-39 years old	280 (69%)	76 (66%)	356 (68.5%)
40-49 years old	48 (12%)	20 (17%)	68 (13.1%)
50-59 years old	4 (1%)	0 (0%)	4 (0.8%)
Education			
Primary education	2 (1%)	0 (0%)	2 (0.4%)
Basic education - 2nd and 3rd cycles	9 (2%)	3 (3%)	12 (2.3%)
Secondary education	93 (23%)	29 (25%)	122 (23.5%)
Higher education	299 (74%)	84 (72%)	383 (73.8%)
Father			
Age			
20-29 years old	42 (10%)	15 (13%)	57 (11.0%)
30-39 years old	271 (67%)	71 (61%)	342 (65.9%)
40-49 years old	85 (21%)	29 (25%)	114 (22.0%)
50-59 years old	3 (1%)	1 (1%)	4 (0.8%)
60-69 years old	2 (1%)	0 (0%)	2 (0.4%)
Education			
Primary education	6 (1%)	1 (1%)	7 (1.3%)
Basic education - 2nd and 3rd cycles	50 (12%)	13 (11%)	63 (12.1%)
Secondary education	169 (42%)	47 (41%)	216 (41.6%)
Higher education	178 (44%)	55 (47%)	233 (44.9%)
Residence			
North	75 (19%)	16 (14%)	91 (17.5%)
Centre	156 (39%)	46 (39%)	202 (38.9%)
Área Metropolitana de Lisboa	114 (28%)	36 (31%)	150 (29.0%)
Alentejo	32 (85)	8 (7%)	40 (7.7%)
Algarve	6 (1%)	6 (5%)	12 (2.3%)
Açores	9 (2%)	2 (2%)	11 (2.1%)
Madeira	11 (3%)	2 (2%)	13 (2.5%)
Only child			
Yes	251 (62%)	75 (65%)	326 (62.8%)
No	152 (38%)	41 (35%)	193 (37.2%)
Children			
Sex			
Male	212 (53%)	52 (45%)	264 (50.9%)
Female	191 (47%)	64 (55%)	255 (49.1%)
Age			
0-6 months	88 (21%)	28 (24%)	116 (22.4%)
7-11 months	15 (4%)	4 (3%)	19 (3.7%)
12-23 months	102 (25%)	28 (24%)	130 (25.0%)
2-3 years old	132 (33%)	31 (27%)	163 (31.4%)
4-6 years old	48 (12%)	23 (20%)	71 (13.7%)
7-10 years old	11 (3%)	1 (1%)	12 (2.3%)
> 10 years old	7 (2%)	1 (1%)	8 (1.5%)
Nursery school attendance			
Yes	225 (56%)	69 (59%)	294 (56.6%)
No	178 (44%)	47 (41%)	225 (43.4%)

Table 2. Parents' opinions regarding the use of a pacifier (n = 519)

	Users (n = 403)	Non-users (n = 116)	Total n (%)
Source of information about pacifiers			
Family and friends	20 (5%)	5 (4%)	25 (5%)
Internet	50 (13%)	30 (26%)	80 (15%)
Doctor	69 (17%)	16 (14%)	85 (16%)
Other health professional	78 (19%)	18 (16%)	96 (18%)
Others	16 (4%)	4 (3%)	20 (4%)
No research was made	170 (42%)	43 (37%)	213 (41%)
Pacifier prevents the occurrence of a health event			
Yes	142 (35%)	28 (24%)	170 (33%)
No	261 (65%)	88 (76%)	349 (67%)
Pacifier has advantages			
Yes	310 (77%)	35 (30%)	345 (67%)
No	93 (23%)	81 (70%)	174 (34%)

Table 2 summarizes parents' opinions regarding the use of pacifiers. When it comes to researching information regarding its use, 213 (41%) parents didn't do any research. The ones that did, chose health professionals as the main source of information, followed by the internet.

In this sample, 403 children used a pacifier and 116 didn't. The major reason for not using a pacifier was infant refusal, in 86 children (74%), followed by parents' decision in 29 children (25%). The reasons for having used a pacifier are shown in Table 3. Most of the parents chose "Others", to then describe a combination of other reasons, the main ones being to soothe and to help falling asleep. Six other reasons were mentioned: to avoid finger sucking (twice), social pressure, the child's sucking reflex, to reduce SIDS risk and to stimulate suction in a premature baby.

The characteristics, use and removal of pacifiers are summarized in Table 3. More than half of the parents (275) took a pacifier to the hospital for child delivery. About 52% of the parents said they used it on a regular basis during the first month of the child's life. Among the children that used a pacifier, 136 children had already gone through the experience of removing it, most of them with ages between 1-3 years old. Parents classified it as very easy in most cases (56%). However, there were cases that parents described as difficult (9,6%) and very difficult (2%)- those occurred in children older than 1 year old.

Most children were full-term babies and had adequate growth and language development, with only 5% of them needing speech therapy (Table 4). The mean age of the first word was 10 ± 3.442 months, with a minimum of 4 months and a maximum of 24 months. There wasn't a statistically significant difference between users and non-users regarding speech development when reported by parents (p = 0.34) or determined by the age of the first word (p = 0.15).

There was a statistically significant difference between users and non-users regarding finger sucking (p = 0.009), with 31% of non-users having had this habit.

As to health-related matters (Table 5), 34% of the children had never been sick and 37% had 1 to 2 disease events. About 36.8% of the children have had at least one event of acute gastroenteritis, with a mean of 0.66 ± 1.092, and 32% had at least one event of acute otitis media, with a mean of 0.82 ± 1.931. There is a statistically significant difference (p = 0.02) between the group of children that used a pacifier with the one that didn't when it comes to the occurrence of acute otitis media. This difference wasn't observed regarding the occurrence of acute gastroenteritis (p = 0.55).

None of the 116 non-users presented sleep abnormalities, determining a statistically significant difference between the groups of children that used and didn't use a pacifier (p = 0.00).

Regarding the existence of dental problems, 40 children out of the 389 that had teeth had dental problems (10.3%). When comparing the group of children that used a pacifier with the one that didn't, there wasn't a statistically significant difference (p = 0.64).

When it comes to feeding (Table 6), 30% of children were exclusively breastfed until the age of 6 months. The most presented reason for premature weaning was the mother not having enough breast milk. Comparing the group of children that used a pacifier during breastfeeding with the one that didn't, a statistically significant difference wasn't found regarding the difficulty in initiating breastfeeding (p = 0.77) nor in breast maladaptation being the reason for stopping breastfeeding before 6 months old (p = 0.62).

Table 3. Pacifiers' use characterization (n = 403)

	Total n (%)
Pacifier to the hospital	
Yes	275 (68%)
No	128 (32%)
Type of pacifier	
Conventional	91 (23%)
Orthodontic	262 (65%)
Doesn't know	50 (12%)
Pacifier with a ring	
Yes	337 (84%)
No	66 (16%)
Pacifier with a ribbon	
Yes	223 (55%)
No	180 (45%)
Reason to use a pacifier	
Soothe	67 (16.6%)
Sleep	69 (17.1%)
Ease pain	4 (1%)
Amuse	2 (0.5%)
All the above	47 (11.7%)
Others	214 (53.1%)
First use of a pacifier	
1st week	207 (51%)
1st month	119 (30%)
< 6 months	60 (15%)
> 6 months	17 (4%)
Reposition of pacifier when the child cries	
Always	28 (7%)
Almost every time	196 (49%)
Occasionally	109 (27%)
Rarely	58 (14%)
Never	12 (3%)
Addition of substance to the pacifier	
Always	1 (0.2%)
Almost every time	6 (1.5%)
Occasionally	33 (8.2%)
Rarely	49 (12.2%)
Never	314 (78%)
Reposition of pacifier during sleep	
Always	8 (2%)
Almost every time	35 (9%)
Occasionally	49 (12%)
Rarely	113 (28%)
Never	198 (49%)
Sleeping position	
Side	206 (51.1%)
Supine	168 (41.7%
Prone	29 (7.2%)
Age of pacifier's removal	
1 month	6 (2%)
< 6 months	19 (5%)
6-11 months	10 (2,5%)
12-23 months	41 (10%)
2-3 years old	50 (12%)
> 3 years old	10 (2.5%)
Still uses a pacifier	267 (66%)

(Continues)

Table 3. Pacifiers' use characterization (n = 403) *(continued)*

	Total n (%)
Pacifier's removal	
Very difficult	3 (1%)
Difficult	13 (3%)
Easy	44 (11%)
Very easy	76 (19%)
Still uses a pacifier	267 (66%)

Discussion

Our study covered all Portuguese regions, resulting in a sample that can give us reliable information, about parent's ideas and beliefs regarding the use and safety of pacifiers. We found no previous studies, in our country, regarding this parenting point of view.

The estimated prevalence of pacifier use in this study was 77.6%. In western countries, 75-85% of parents admitted to using a pacifier[2]; This massive use can be explained by the calming effect on the baby's cry, the help it provides in sleeping, reducing stress and pain, as identified by the parents in this study. All these problems can cause great anxiety, especially in first-time parents, or those of newborns, therefore leading to an early pacifier use[4]. Accordingly, in our study, 53% of parents took a pacifier to the maternity ward for child delivery and half of them made use of it in the 1st week after birth. However, other reasons for using a pacifier were also listed, such as a way of avoiding finger sucking, social pressure, because of the child's non-nutritive sucking reflex, to prevent SIDS and to stimulate suction in a premature baby, all these commonly described in other studies[3]. A 2017 Cochrane Review[5] stated that there was no randomized control trial evidence on which to support or refute the use of pacifiers for the prevention of SIDS. On the other hand, breastfeeding for at least two months, especially when breastfeeding is exclusive, is protective against SIDS[6].

The reasons parents identified for avoiding pacifiers were infant refusal, parents' decision, and maxillofacial malformation. Other reasons described in the literature were also fear of attachment to the pacifier, nipple confusion, hygiene, and dental and growth problems[7].

Although the use of pacifiers is something they worry about, most parents (41%) didn't seek any information about it. Those who had information about the use of pacifiers, obtained it either from health professionals (34%) or via internet (15%), with the latter having a greater expression on those parents whose child didn't use a pacifier.

Table 4. Child's development (n = 519)

	Users (n = 403)	Non-users (n = 116)	Total n (%)	p value
Development				
Pregnancy duration				
< 37 weeks	25 (6%)	8 (7%)	33 (6.4%)	
≥ 37 weeks	378 (94%)	108 (93%)	486 (93.6%)	
Adequate growth				
Yes	368 (91%)	112 (97%)	480 (92.5%)	
No	35 (9%)	4 (3%)	39 (7.5%)	
Speech development problems				0.34
Yes	24 (6%)	4 (3%)	28 (5%)	
No	226 (56%)	64 (55%)	290 (56%)	
Doesn't speak	153 (38%)	48 (42%)	201 (39%)	
Finger sucking				
Yes	82 (20%)	36 (69%)	118 (23%)	
No	321 (80%)	80 (31%)	401 (77%)	

Table 5. Child's health aspects (n = 519)

	Users (n = 403)	Non-users (n = 116)	Total n (%)	p value
Health				
Disease events in a year				
None	135 (34%)	41 (35%)	176 (34%)	
1-2 times	142 (35%)	50 (43%)	192 (37%)	
3-4 times	78 (19%)	17 (15%)	95 (18.3%)	
> 4 times	48 (12%)	8 (7%)	56 (11%)	
Acute otitis media				0.02
Yes	139 (65%)	27 (77%)	166 (32%)	
No	264 (35%)	89 (23%)	353 (68%)	
Acute gastroenteritis				0.55
Yes	151 (63%)	40 (65%)	191 (36.8%)	
No	252 (37%)	76 (35%)	328 (63.2%)	
Speech therapy				
Yes	19 (5%)	8 (7%)	27 (5%)	
No	231 (57%)	60 (52%)	291 (56%)	
Still doesn't speak	153 (38%)	48 (41%)	201 (39%)	
Dental problems				0.64
Misalignment	4 (1%)	3 (2,5%)	7 (1.3%)	
Cavities	6 (2%)	4 (3%)	10 (1.9%)	
Malocclusion	15 (4%)	3 (2.5%)	18 (3.5%)	
Others	5 (1%)	0 (0%)	5 (1%)	
No problems	273 (67%)	76 (66%)	349 (67.2%)	
Still no teeth	100 (25%)	30 (26%)	130 (25%)	
Preferential breathing through				
Mouth	28 (7%)	7 (6%)	35 (6.7%)	
Nose	295 (73%)	85 (73%)	380 (73.3%)	
Doesn't know	80 (20%)	24 (21%)	104 (20.0%)	
Sleep abnormalities				0.00
Sleeping with mouth open	92 (23%)	0 (0%)	92 (17.7%)	
Snoring	26 (6%)	0 (0%)	26 (5%)	
Drooling	23 (6%)	0 (0%)	23 (4%)	
Waking up thirsty	22 (5%)	0 (0%)	22 (4%)	
None of the above	240 (60%)	116 (100%)	356 (68.6%)	

Table 6. Child's feeding habits (n = 519)

	Users (n = 403)	Non-users (n = 116)	Total n (%)	p value
Feeding				
Feeding until 6 months old				
Breastfeeding	223 (55%)	97 (84%)	320 (62%)	
Formula feeding	29 (7%)	3 (2%)	32 (6%)	
Breast + formula feeding	151 (38%)	16 (14%)	167 (32%)	
Exclusive breastfeeding				
Until leaving the maternity	13 (3%)	2 (2%)	15 (2.9%)	
Until the 1st week	31 (8%)	5 (4%)	36 (6.9%)	
Until the 1st month	28 (7%)	4 (3%)	32 (6,2%)	
Until the 2nd month	28 (7%)	2 (2%)	30 (5.8%)	
Until the 4th month	93 (23%)	16 (14%)	109 (21%)	
Until the 6th month	107 (26%)	53 (46%)	160 (30.8%)	
> 6 months	59 (15%)	31 (26%)	90 (17.3%)	
Never	44 (11%)	3 (3%)	47 (9.1%)	
Difficulty in initiating breastfeeding				0.77
Yes	164 (41%)	35 (70%)	199 (38%)	
No	239 (59%)	81 (30%)	320 (62%)	
Reason for stopping breastfeeding before 6 months old				0.62
Little weight gain	9 (2%)	1 (1%)	10 (2%)	
Insufficient breast milk	68 (17%)	6 (5%)	74 (13%)	
Mum had to go back to work	27 (7%)	7 (6%)	34 (6%)	
Breast maladaptation	30 (7%)	1 (1%)	31 (5%)	
Mum's option	17 (4%)	4 (3%)	21 (4%)	
Others	16 (4%)	1 (1%)	17 (3%)	
Still breastfeeds	236 (59%)	96 (83%)	332 (57%)	
Pacifier use during breastfeeding				
Yes	356 (88%)	0 (0%)	356 (69%)	
No	47 (12%)	116 (100%)	163 (31%)	

Choosing a pacifier may be difficult for parents because the offer is so vast, and doctors are often confronted with questions regarding pacifiers' characteristics. One study[8] concluded that orthodontic pacifiers have less impact on open bite when compared to conventional pacifiers, although other studies[9] haven't found any differences. It is recommended that the pacifier has a ring, so it can be pulled in case of choking, and a ribbon that should be attached to the child's clothes, no bigger than 22cm to avoid suffocation[10]. As it was observed, Portuguese parents followed these recommendations, using orthodontic (65%) pacifiers, with a ring (84%) and a ribbon (55%).

Most parents (49%) reposition the pacifier almost every time when the child cries, and 7% do it every time. This may be because the baby's cry can cause great anxiety. On the contrary, most parents (49%) never reposition the pacifier during sleep, which is in accordance with recommendations[11]. Also, on the positive side, we found that almost 93% of children sleep in a supine or side position, which is in line with current guidelines regarding sleep safety[5].

Most parents never or rarely add a substance to the pacifier, but some added sugary substances to the pacifier, probably to diminish the possibility of refusal. This practice is not recommended because of its effects on future eating patterns and risk of botulism in certain parts of the world[11].

Non-nutritive sucking can also be manifested by finger sucking. There was a difference between groups regarding finger sucking (p = 0.009), with non-users more frequently developing this habit. Exclusive breastfeeding also reduces non-nutritive sucking habits[12].

Removing pacifiers may cause anticipatory anxiety to parents, that try to plan for it. In our study parents considered the removal an easy process. Children were between the ages of 1 and 3 in 67% of cases. The American Academy of Pediatrics and the American Academy of Family Physicians recommend that pacifiers should be avoided after the age of 6 months because

of the risk of otitis media and discourage its use after 4 years old because of dental malocclusions. The delay of the removal age may have an impact on the development of stomatognathic structures and functions, essential for language development[1].

A major source of concern for parents and health professionals is the effect of the use of pacifiers on the child's development and health. No differences were found regarding premature weaning from breastfeeding between users and non-users. There is divergent evidence in this area, with a study demonstrating no differences in premature weaning from breastfeeding until 3 months old between full-term, exclusively breastfed babies that used and didn't use a pacifier[13] and another demonstrating a premature weaning from breastfeeding and formula feeding[4]. The use of pacifier may also be associated with several unfavorable behaviors during breastfeeding regarding positioning, attachment, suction adequacy, and baby's responses[4]. In addition, pacifier use has been associated with acute otitis media and there is also some evidence reporting association with dental infection and respiratory and gastrointestinal symptoms[2]. In our study, a difference was observed between users and non-users regarding acute otitis media (p = 0.02), but not acute gastroenteritis (p = 0.55). A topic that still lacks solid evidence are the effects of pacifier use on speech. A recent study analyzed the duration and frequency of pacifier use in children, finding no clear association with speech abnormalities[14]. Our study also presented no difference between users and non-users when analyzing the existence of speech problems, including speech delay. Nonetheless, some of these difficulties may yet not be seen by parents and become apparent in the future, for this questionnaire was also answered by parents of very young children.

We found no difference in dental problems between users and non-users but there seems to be some evidence supporting the association between the use of pacifier and anterior open bite and posterior crossbite[8]. There is also a correlation between the use of pacifiers and smaller intercanine distance of the upper arch, mean overjet, half-open or open lip posture and unexpected contraction during mastication, affecting the harmonious development of the orofacial structures[15]. It was also reported a higher frequency of Angle's class II in females and class III in males in association to the use of pacifiers[16]. Although dental effects were noted in children older than 2 years, the most significant changes were seen in children older than 4 years, therefore the use of pacifier should be discouraged after 4 years of age[2]. Another alteration that is reported in association with the use of pacifiers is mouth breathing, and for

each year that pacifier removal is delayed, mouth breathing diagnosis is increased by 25%[15]. No difference between users and non-users was found in our study in this regard. However, when comparing the two groups for sleep abnormalities (mouth breathing, snoring, drooling and thirsty when waking), there was a significant difference (p = 0.00). These changes can be influenced by other factors that weren't evaluated, such as the presence of nasal obstruction, resulting in the need for future studies.

We found several limitations in our study that prevents us from making a population inference.

One is the small number of participants in a convenience sample. Another is the identification of health-related variables and diagnosis being self-reported which can potentially lead to over or underestimation (ex: otitis media, gastroenteritis, late language development, dental problems) and recall bias. Additionally, 26% of parents in our sample are health professionals, and 73.8% of mothers and 44% of fathers had higher education, which is a much higher proportion than in the general population.

We consider very important that parents are given information about the pros and cons of pacifier use so they can make an individualized and informed decision and be prepared to minimize possible problems related to pacifier use.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Breastfeeding knowledge and attitudes of health professionals attending lactating mothers in a secondary care Portuguese hospital: a cross-sectional study

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Abstract

Introduction and Objectives: Despite proven benefits of breastfeeding for the health of the mother-child dyad, breastfeeding rates worldwide remain suboptimal. The role of health workers is critical to breastfeeding process. However, evidence suggests that some lack the skills to adequately counsel breastfeeding mothers. Our aim was to assess the knowledge and attitudes of health professionals toward breastfeeding. **Methods:** We used a validated questionnaire CAPA (*Competència en l'Atenció Primària sobre Alletament*) to assess the level of competence and attitudes towards breastfeeding among health professionals involved in supporting breastfeeding mothers at a secondary care Portuguese Hospital. **Results:** The analysis included 81 participants (48 physicians (39 pediatricians/pediatric residents and 9 obstetricians and gynecologists/obstetrics and gynecology residents) and 33 nurses). The mean score (125 ± 11) was suboptimal. A statistically significant difference was found between specialities (p = 0.034), with pediatrics scoring the highest. **Discussion:** Since only half of health professionals felt totally confident in giving breastfeeding advice, they would benefit from breastfeeding education programs to optimize care for infants and their mothers.

Keywords: Breastfeeding. Breastfeeding knowledge. Nurses knowledge.

Conhecimentos e atitudes sobre aleitamento materno dos profissionais de saúde que prestam cuidados a mães lactantes num hospital secundário português: um estudo transversal

Resumo

Introdução e objetivos: Apesar dos comprovados benefícios do aleitamento materno na saúde da díade mãe-filho, as taxas de aleitamento materno em todo o mundo permanecem inferiores às recomendações. O papel dos profissionais de saúde é fundamental no processo de amamentação. No entanto, as evidências sugerem que estes profissionais carecem de competências no aconselhamento adequado às mães que amamentam. O nosso objetivo foi avaliar o conhecimento e as atitudes dos profissionais de saúde em relação ao aleitamento materno. **Métodos:** Utilizou-se um questionário validado CAPA (Competència en l'Atenció Primària sobre Alletament) para avaliar o nível de competência e atitudes em relação à amamentação entre os profissionais de saúde envolvidos no apoio a mães lactantes de um Hospital Português nível II. **Resultados:** A análise incluiu 81 participantes (48 médicos [39 pediatras/internos de pediatria e 9 obstetras e ginecologistas/internos de obstetrícia

e ginecologia] e 33 enfermeiros). A pontuação média (125 ± 11) foi inferior à ideal. Verificou-se uma diferença de pontuações estatisticamente significativa entre as especialidades (p = 0,034), a pediatria com pontuação mais elevada. **Discussão:** Como apenas metade dos profissionais de saúde se sente totalmente confiante em orientar mães na amamentação, poderiam beneficiar de programas de treino de forma a otimizar o seu atendimento aos bebés e suas mães.

Palavras-chave: Aleitamento materno. Conhecimentos sobre aleitamento materno. Conhecimentos de médicos e enfermeiros.

Keypoints

What is known
– The role of health workers is critical to the breastfeeding process.
– Mandatory breastfeeding education programs could be essential to improve the knowledge of our health care workers and increase breastfeeding rates.

What is added
– Our health workers' knowledge about breastfeeding was suboptimal and half of them did not feel completely confident in guiding mothers in breastfeeding.

Introduction

The American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACOG) and the World Health Organization (WHO) recommend that infants receive human milk exclusively for the first six months of life and continue up to two years or beyond with appropriate complementary foods[1-4]. Breastfeeding, even if partial or for a shorter period than desirable, maintains a beneficial effect when compared to exclusive feeding with infant formula[5].

Human milk has a unique composition, with antimicrobial, anti-inflammatory and immuno-regulatory agents, that contribute to the developing immune system of the child[6,7]. Data reveal that, in the second year of life, human milk continues to be an important source of macronutrients and immunologic factors[6]. The long-term benefits include reduced risk of re-hospitalization due to infectious diseases and brain and neurocognitive development. The health benefits are also extensive for maternal outcomes as evidence demonstrates an inverse relationship between breastfeeding and breast, ovarian, endometrial and thyroid cancer and a reduced risk of hypertension and diabetes[5,7].

Breastfeeding is one of few positive health-related behaviors that is less frequent in high-income countries compared to low and middle-income countries; in high-income countries, more than 1 in 5 babies are never breastfed[8].

It is reported that maternity leave is one of the most important measures for longer breastfeeding duration[9]. According to the European Union (EU) directives, women should have the right to maternity leave of at least 14 weeks. Portugal has one of the shortest maternity leave in the European Union, it is possible to take 120 (17 weeks) or 150 days of leave (21 weeks): 120 days are paid at 100% and 150 days at 80%[10].

A Portugal health survey in 2014 reported a positive trend toward an increase in women exclusively breastfeeding, with this trend more pronounced in continental Portugal than in the autonomous regions (Madeira and Azores). Nevertheless, the rate of exclusive breastfeeding was lower than the recommended until 6 months. In the 3rd month, 56% of infants were exclusively breastfed, in the 4th month, this percentage decreased to 49% and in the 6th month, the percentage declined to 32%[11].

In our hospital, over a three-year period (2019 to 2021), 86% of newborns were fed breast milk in the first hour of life. However, this percentage decreased to 50% at the time of discharge from the nursery, at which time 46% were fed breast milk and formula and 4% were fed exclusively with formula.

WHO and United Nations International Children's Emergency Fund (UNICEF) have proposed implementing a program with Ten Steps to Successful Breastfeeding applied to all institutions providing maternity and newborn assistance worldwide. The program includes measures that ensure professionals involved in breastfeeding have sufficient knowledge, competence and skills to support it[1,12,13]. Nurses, pediatricians, obstetricians and gynecologists play a critical role in hospitals as breastfeeding advocates. However, health professionals do not always receive adequate breastfeeding education to effectively help mothers[13-20]. Midwives, due to specific professional training, commonly form the professional group with the best expertise in breastfeeding[15,16].

In 2018, the Commission for Promotion, Protection and Support of Breastfeeding was founded at São Sebastião

Hospital. The team consists of 14 members, including paediatric/neonatology and gynaecology/obstetrics physicians, nurses and nurse assistants. This commission has invested in the training of health professionals through multiple breastfeeding courses, webinars and conferences. In view of these measures, our primary objective was to assess the knowledge and attitudes of health professionals toward breastfeeding. The secondary objective was to identify which group of health professionals is less able to support breastfeeding and should undertake more training interventions.

Methods

Study Population

We carried out a cross-sectional study conducted at a secondary care Portuguese Hospital (São Sebastião Hospital) during the period of January to March 2022. The target population was obstetrics/gynecology and pediatric health professionals (specialists, residents and nurses), participation was voluntary with informed consent. A total of 81 health professionals completed the questionnaire.

Questionnaire description

A translated and adapted version of CAPA questionnaire (*Competència en l'Atenció Primària sobre Alletament*) was used to assess basic competence about breastfeeding. This instrument was designed by Pol-Pons et al. and it is a self-reported questionnaire originally written in Catalan and previously translated to Portuguese[15].

The CAPA questionnaire is an instrument validated in Spain to assess the breastfeeding knowledge among primary care professionals involved in supporting breastfeeding mothers, with high levels of internal consistency, validity and reproducibility[16].

The original questionnaire contains 24 questions (Supplement 1) in which the answers are scored on a 6-point Likert scale, where 1 corresponds to "totally disagree" and 6 to "totally agree". The maximum score (6 points) was obtained when items 1-4, 11, and 13-24 were answered "totally agree", and items 5-10 and 12 were answered "totally disagree". The final score, indicating competence about breastfeeding, was estimated as the sum of the points obtained on all items. The cut-off point indicating a good level of competence about breast feeding was established as 129 points[15,16].

We used the Portuguese translation of a study[15] and, for validation, asked a group of three health professionals

(a neonatologist, a pediatric nurse, and a pediatric resident) to perform a semantic and content analysis, including clarity, absence of ambiguity, absence of technical terms, and general comprehensibility. This strategy is commonly used to ensure face and content validity, i.e. the extent to which the questionnaire adequately represents the topic under study (content validity), in a manner that is understandable and relevant for potential respondents (face validity)[21].

Six questions were added to characterize the sample, in terms of age, gender, professional group (physician/nurse), specialty (pediatricians/pediatric residents and obstetricians and gynecologists obstetricians and gynecologists' residents) and resident year. Four other questions were added to ascertain the perception and confidence in guiding pregnant women and mothers in breastfeeding.

This study was approved by the ethics committee of our hospital. Completion of the questionnaire was confidential, voluntary, and anonymous.

Data analysis

Data was analyzed using SPSS Statistics version 28®. We employed descriptive statistics to characterize dependent and independent variables. We compared physician and nurses' knowledge and attitudes using Student's t-test. The Levene's test was used to test for homogeneity of variances. If Levene's Test was statistically significant ($p < 0.05$) null hypothesis of equal population variances was rejected.

Results

This study included 81 health professionals with an average age of 38 years ± 8.9, the majority were female (95%). 59% (n = 48) of the sample were physicians and 41% (n = 33) were nurses. As for medical specialty, 81% (n = 39) were pediatricians/pediatric residents and 19% (n = 9) were OG/obstetrics/gynecology residents.

The score on basic knowledge about breastfeeding, in which the maximum possible score was 144, ranged from 88 to 141, with a mean of 124.6 ± 10.6 (Fig. 1).

Although nurses achieved a lower median score (122.7 ± 12.5) compared to physicians (125.9 ± 9), no statistically significant difference was found between the two group of professionals (p = 0.19) (Fig. 2).

However, when comparing medical specialties (pediatrics vs. obstetrics and gynecology), a statistically significant difference was found (p = 0.034), with obstetrics and gynecology scoring the lowest value (120.2 ± 10.3) and pediatrics the highest (127.2 ± 8.3) (Fig. 3).
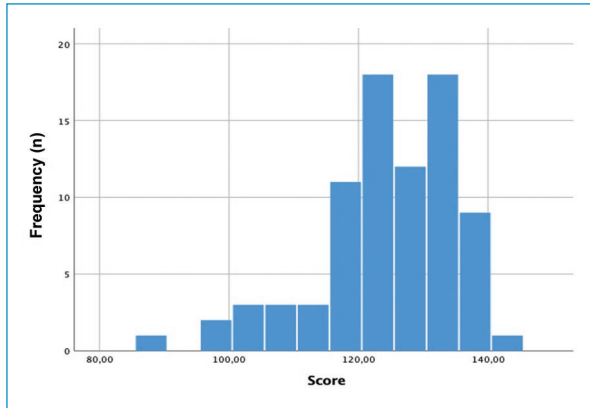
Figure 1. Score distribution.
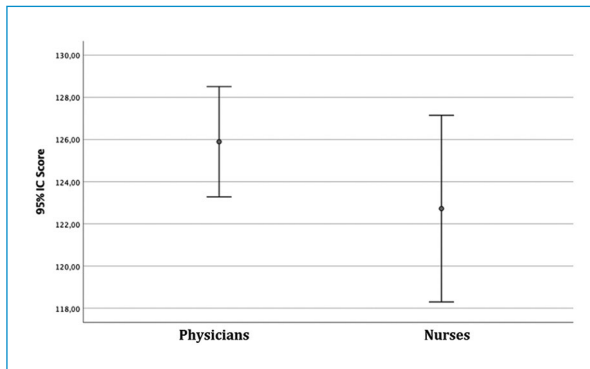
Figure 2. Score according to profession (physicians vs nurses).
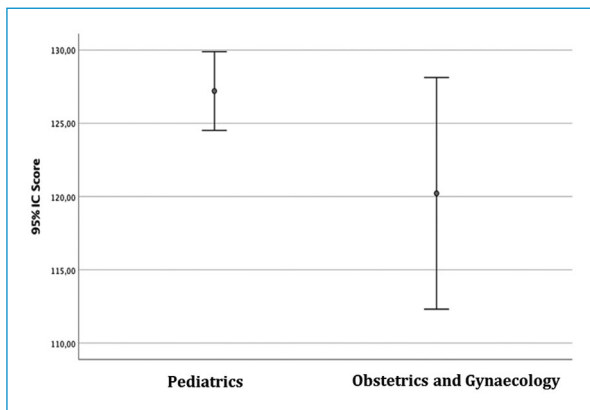
Figure 3. Score according to specialty (pediatrics vs. obstetrics and gynecology).

Figure 4. Question 25 (Q25): do you consider that it is the responsibility of the doctor to guide mothers in breastfeeding?
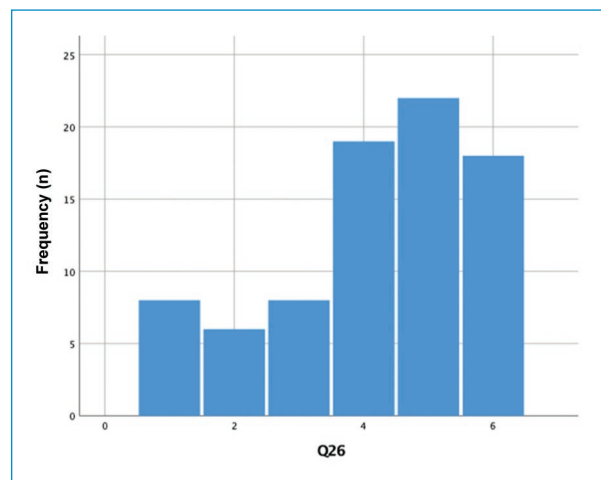
Figure 5. Question 26 (Q26): do you consider that it is the responsibility of the nurse to guide mothers in breastfeeding?

When asked if they consider that it is the physician's responsibility to guide mothers in breastfeeding (Fig. 4 - Question 25), 18.5% answered that they "totally agree" (all were doctors), with an average of 3.75 in the answers.

In the question if they consider that it is the nurse's responsibility to guide mothers in breastfeeding (Fig. 5 - Question 26), 22% answered that they "totally agree" (72% were doctors and 28% were nurses), with an average of 4.37 in the answers.

When asked if they feel confident in advising a pregnant woman or mother about breastfeeding (Fig. 6 - Question 27), although the majority feel confident overall (93%), only 50% feel completely confident, with an average of 5.22 among the answers.
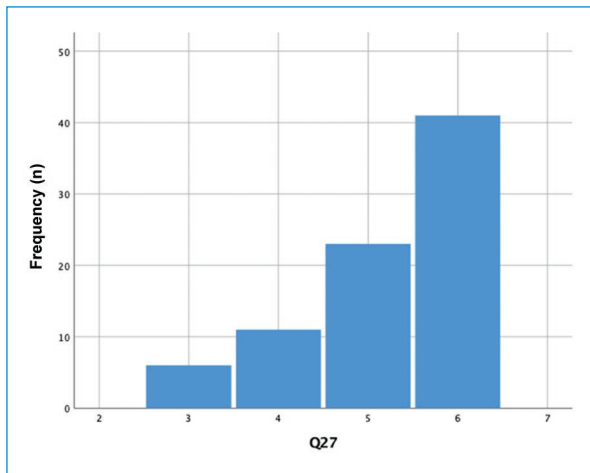
Figure 6. Question 27 (Q27): do you feel confident to advise a pregnant woman or mother about breastfeeding?

Figure 8. CAPA-Questionnaire score (mean and 95% confidence interval) obtained by professional groups attending lactating mothers in primary care.[16]

Figure 7. Question 28 (Q28): do you consider that the responsibility for guiding mothers about breastfeeding belongs to the entire team involved in the care of the mother and baby?

When asked if they believe that the responsibility for breastfeeding counselling falls on the entire team involved in the care of mother and child (Fig. 7 - Question 28), 86.4% "totally agree", with an average of 5.81 among the answers. The gender, profession and specialty distribution is resumed in Tables 1-3.
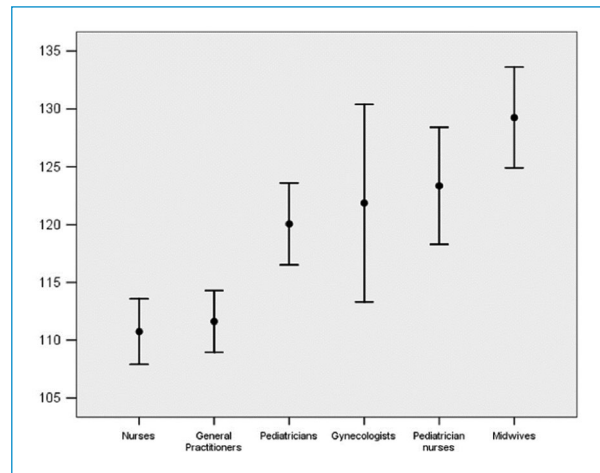
Discussion

In the CAPA questionnaire, the cut-off point indicating a good level of competence towards breastfeeding,

was concluded to be 129[22]. Therefore, the mean score obtained in our study was suboptimal (125 ± 11 points). Our pediatric physicians mean score is slightly superior to what is discriminated in that study[16], however, Obstetrics and Gynecology physicians average score is inferior, as shown in Figure 8.

As described in other reports, the average knowledge level of pediatric health professionals was significantly higher than Obstetrics and Gynecology health professionals. This finding may be related to the fact that pediatricians are most frequently confronted with practical questions related to breastfeeding[23,24]. In our study, the score did not differ significantly between professional groups (physicians and nurses) contradicting what is published by others[16].

In a recent study conducted in Portugal, it was found that students in the medical course do not acquire enough knowledge[15]. Therefore, it is recommended that greater emphasis be placed on breastfeeding education in medical school, beginning in the general year, as physicians in all specialties are required to have a minimum of competency in breastfeeding. It is of particular concern that professionals directly involved with mother and child have suboptimal knowledge of this topic[14,15,23,24].

There is ample evidence that increased education and support for parents during pregnancy or postpartum improves breastfeeding initiation and continuation[14].

Despite all the measures taken to improve attitudes and knowledge about breastfeeding, especially the foundation of the Commission for the Promotion,

Table 1. Gender distribution

	Frequency (n)	Valid percentage (%)
Female	77	95.1
Male	4	4.9
Total	81	100

Table 2. Profession distribution

	Frequency (n)	Valid percentage (%)
Physician	48	59.3
Nurse	33	40.7
Total	81	100

Table 3. Specialty distribution

	Frequency (n)	Valid percentage (%)
Pediatricians	39	81.3
Obstetricians and gynecologists	9	18.8
Total	48	100

Protection and Support of Breastfeeding in our Hospital, the results fell short in relation to our expectations: 50% of health professionals do not feel completely confident in dealing with breastfeeding problems[13,18,20]. In another study, 74.2% of pediatricians reported overall confidence in breastfeeding counseling skills[23].

In our study, 86.5% of health professionals believe that the responsibility for breastfeeding counselling lies with the entire team involved in the care of mother and child. Only 22% think that nurses are responsible for it and 18.5% think it is the responsibility of physicians. All health professionals involved in the care of mother and child should be able to offer breastfeeding counselling. Training programs for health professionals appear to improve knowledge and attitudes about breastfeeding[13]. Encouragement to breastfeed should come through improvements and changes in all professional teams. Changes through the implementation of the ''Ten Steps to Successful Breastfeeding'' program (Table 4) reinforce effective support for breastfeeding and are also one of the prerequisites for the designation, attributed to hospitals, as a Baby-Friendly Hospital[1,12,25].

Table 4. WHO/UNICEF ten steps to successful breastfeeding[25]

1. Have a written breastfeeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in the skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within a half-hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.
6. Give newborn infants no food or drink other than breast milk, unless medically indicated.
7. Practice rooming-in: allow mothers and infants to remain together 24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

Limitations of the study include a low response rate, especially in the OG group. However, the sample is statistically representative of our institution. In addition, we may see as a limitation the fact that this questionnaire is validated for primary health care, but was applied in a secondary hospital.

It is essential that health professionals have a positive attitude in relation to breastfeeding to provide women with the information they require. All institutions should invest in mandatory training programs in breastfeeding, namely with role play situations, to improve knowledge and attitudes about breastfeeding and increase confidence in supporting and guiding breastfeeding mothers[14,15,23,24].

Our data show that, despite our efforts, we still have a long way to go. At the same time, since various organizations recommend exclusive breastfeeding until the sixth month of life, extending maternity leave during this period, would have a positive effect on breastfeeding.

This validated questionnaire could be used at a national level to assess the knowledge of other professionals involved in breastfeeding, in order to obtain an accurate and updated state of the art in Portugal.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with

the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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The path made and where to go: trends in the neonatal mortality rate. A cross-sectional study

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Abstract

Introduction: Neonatal mortality is an indicator of maternal and child health, which reflects the level of pre- and post-natal care. The objective of the present study was to determine the neonatal mortality rate, its trend, and respective causes in a Neonatal Intensive Care Unit. **Methods:** Retrospective, descriptive observational study that included newborns who died between 1992 and 2020 in a differentiated perinatal support unit. **Results:** There were 390 deaths (mortality rate 5.7%). Fifty per cent of deaths occurred in the early neonatal period; 77% in premature infants. The trend in neonatal mortality decreased over the decades, mainly due to early and late neonatal mortality. Post-neonatal mortality remained stable. The main causes of death were prematurity-related organ dysfunction (39%), infections (24%), and congenital anomalies (16%). There was a decrease in the proportion of deaths from congenital anomalies and an increase in the proportion of infections. An autopsy was performed in 176 newborns (45%). **Discussion:** This study offers a long period of analysis of mortality rates with more extent data from a particular neonatal population. The decrease in neonatal mortality rates and deaths due to congenital anomalies reflect the progress achieved in prenatal diagnosis and differentiated prenatal and postnatal healthcare. On the other hand, infection remained one of the main causes of late neonatal and post-neonatal death. Analysis of neonatal mortality has the potential to enable a refined clinical practice. Focus on post-neonatal and infection-related mortality should be the next priorities in the improvement of neonatal care.

Keywords: Early-neonatal mortality. Post-neonatal mortality. Neonatal intensive care. Prematurity.

O caminho percorrido e para onde ir: evolução da taxa de mortalidade neonatal. Um estudo transversal

Resumo

Introdução: A mortalidade neonatal constitui um indicador de saúde materno-infantil, que reflete o nível de cuidados pré e pós-natais. O objetivo do presente estudo foi determinar a taxa de mortalidade neonatal, a sua tendência e as respetivas causas numa Unidade de Cuidados Intensivos Neonatais. **Métodos:** Estudo retrospetivo, observacional e descritivo. Incluídos recém-nascidos que faleceram entre 1992 e 2020 numa unidade de apoio perinatal diferenciado. **Resultados:** No período de estudo ocorreram 390 óbitos (taxa de mortalidade de 5.7%). Cinquenta por cento das mortes ocorreram no período neonatal

precoce; 77% em prematuros. A taxa de mortalidade neonatal apresentou uma tendência decrescente ao longo dos anos, maioritariamente devido à diminuição da mortalidade neonatal precoce e tardia. A mortalidade pós-neonatal manteve-se estável. As principais causas de morte foram: complicações da prematuridade (39%), infeções (24%) e anomalias congénitas (16%). Verificou-se uma diminuição da proporção de mortes por anomalias congénitas, contrariamente às infeções cuja proporção aumentou. Foi realizada autópsia em 176 recém-nascidos (45%). **Discussão:** Neste estudo apresentamos um período longo de análise da taxa de mortalidade de uma determinada população neonatal. A diminuição da taxa de mortalidade neonatal e dos óbitos por anomalias congénitas refletem os progressos alcançados a nível de diagnóstico pré-natal e de cuidados pré e pós-natais diferenciados. Por outro lado, a infeção manteve-se como uma das principais causas de morte neonatal tardia e pós-neonatal. A análise da mortalidade neonatal, tem potencial para possibilitar uma prática clínica mais apurada. O foco na mortalidade pós-neonatal e infeção devem ser as próximas prioridades para uma melhoria dos cuidados neonatais.

Palavras-chave: Mortalidade neonatal precoce. Mortalidade pós-neonatal. Cuidados intensivos neonatais. Prematuridade.

Keypoints

What is known
– Neonatal mortality results from a complex relationship between biological, social and health care variables.
– Neonatal mortality accounts for 2/3 of child mortality.
– Premature newborns and/or those with low birth weight are at greatest risk of neonatal mortality.

What is added
– There has been a decrease in the neonatal mortality rate in recent years due to advances in pre- and postnatal care.
– Infection and post-neonatal mortality are areas of possible intervention.
– Pathology examination can offer more answers and enable a better future care.

Introduction

Neonatal mortality, defined as death within the first 28 days of life, results from a complex relationship between biological, social, and health care variables[1]. It constitutes an important maternal and child health indicator, reflecting the healthcare provided to the neonatal population. Globally, in 2019, 2.4 million children died in the first month of life, which is equivalent to 6.700 deaths daily[2]. Neonatal mortality accounts for 2/3 of child mortality[3,4]. Premature newborns (NB) and/or those with low birth weight (LBW) are those at greatest risk, accounting for 85% of neonatal deaths[2,3].

Advances of technical and scientific knowledge, with an increase in the quality of perinatal and neonatal care, resulted in a reduction in neonatal mortality in recent decades. Between 1990 and 2019, there was a 52% reduction in neonatal mortality worldwide (from 37 deaths/1000 births to 17 deaths/1000 births)[2]. Portugal has followed this downward trend with a reduction from 6.9 to 1.9 deaths/1000 births in the same period[2]. In developing countries, most neonatal deaths occur from preventable causes such as infections or perinatal asphyxia[5-7]. In developed countries such as Portugal, published data are scarce, focusing mainly on the circumstances of death and end-of-life care[8,9].

The present study was conducted at a Neonatal Intensive Care Unit (NICU) with a differentiated perinatal support. The main objective was to determine the mortality rate (MR), its trend, and the respective causes of death in the last three decades. The specific objectives were to characterise data on pregnancy and delivery; analyse the causes of death according to gestational age (GA) and birth weight (BW); assess the distribution of causes of death by time of death; identify the percentage of autopsies performed; analyse the concordance between clinical and pathological diagnoses and compare the results with national and international published data.

Material and methods

Retrospective and descriptive observational study with the data obtained from the database/clinical records of the NICU. All NB who were admitted and died between January 1, 1992, and December 31, 2020, were included. All stillbirths and NBs who died in the delivery room were excluded. Data were obtained by consulting the clinical records of the NB and the mother, death certificate and autopsy reports. The information collected included data on maternal medical history, gestation, and delivery. From the NB, data were obtained from sex, GA, BW and weight at death, chronological and corrected age at death, cause of death and pathology diagnosis. When information was incomplete, subtotals were presented for each variable analysed.

The study was approved by the Ethics Committee.

The manuscript was written according to the STROBE checklist.

Definitions and classifications

In recent years, improvement in neonatal intensive care may have led to a biased definition of neonatal death due to the exclusion of patients who remained hospitalised and died after 28 days of life. Thus, the term *neonatal-related deaths*, introduced by Phibbs, et al.[10] includes all neonatal deaths and those occurring between 28 days of life and one year, if the child remained hospitalized. Therefore, neonatal deaths were categorised as follows: early neonatal death (first 6 days of life), late neonatal death (between 7 and 27 days of life) and post-neonatal death (after 28 days of life).

In this study, the causes of death were classified using an adaptation of the Wigglesworth scale[11]. Five groups were defined: group 1- infections; group 2- congenital anomalies; group 3- immaturity/conditions associated with prematurity (hyaline membrane disease, necrotizing enterocolitis, central nervous system (CNS) haemorrhage, pulmonary haemorrhage, extreme immaturity, other causes of death resulting from prematurity complications); group 4- asphyxia during labour; group 5- other causes not included in the previous groups.

The concordance between clinical and pathological diagnosis was evaluated using the modified Goldman classification (Table 1)[12].

Statistical analysis

Data were processed using Excel Windows 7®, SPSS (Statistical Package for Social Sciences)® version 24 and Rstudio version 1.4.1717. The analysis of the annual trend of neonatal mortality and respective causes of death was performed using the chi-square test for trends in proportions. A significance level of $p < 0.05$ was considered.

Results

During study period, 6816 NB were admitted, corresponding to an average of 235 admissions/year, of which 28% (n = 1884) were very low birth weight (VLBW) NB.

Of the 6816 NB admitted, 390 deaths were registered, which corresponded to a MR of 5.7%. Among the deceased NB, 204 (52%) were male. Median GA was 29 weeks (minimum 22 and maximum 42 weeks). Three hundred (77%) were premature NB, 54% (163/300) of which were extremely premature. Median birth weight (BW) was 1092g (minimum 420 and maximum 4400g) and 237 (60%) NB were VLBW.

Table 1. Concordance between clinical and pathological diagnosis according to modified Goldman classification

Class	Description
IA	Diagnosis that, if detected before death, would probably have led to change in management that might have resulted in cure or prolonged survival
IB	Diagnosis with significant implications for future genetic advice
II	Diagnosis that, if detected before death, would probably not have led to change in management or survival because: – No appropriate therapy was available at the time – Appropriate therapy was given even though the diagnosis was unknown at the time – Patient had acute cardiopulmonary arrest that was appropriately managed, but patient did not survive for definitive management – Patient had "do not resuscitate" status
III	Diagnosis that may or may not have been related to main disease process and was contributory cause of death
IV	Diagnosis unrelated to outcome and may or may not have affected the patient's prognosis
V	Complete concordance between diagnosis before death and findings at autopsy

Regarding maternal, pregnancy and delivery data: the median maternal age was 28 years (minimum 14 and maximum 47 years) and in 44 cases (14%; 44/312) a relevant medical history was recorded (Table 2). In 73 cases (23%; 73/312) there was a history of miscarriage and in 13 cases (4%; 13/312) a history of previous fetal or neonatal death. Three hundred and twenty (82%) pregnancies were monitored and 322 (83%) were single pregnancies. In 312 cases (80%) there was a history of at least one complication during pregnancy and the most frequent were: threatened preterm delivery in 183 cases (58%; 183/312), premature rupture of membranes in 65 cases (20%; 65/312), fetal growth restriction in 48 cases (15%; 48/312), clinical suspicion of chorioamnionitis in 37 cases (11%; 37/312), placental abruption in 29 cases (9%; 29/312), pre-eclampsia in 28 cases (9%; 28/312) and gestational diabetes in 16 cases (5%; 16/312). In 124 cases (44%; 124/280), a scheme of prenatal corticosteroids for pulmonar maturity stimulation was performed. This procedure increased over the years of study (p < 0.01).

Evolution of neonatal mortality

During the study period, 195 NB (50%) died in the early neonatal period, 153 (39%) in the late neonatal period and 42 (11%) in the post-neonatal period. MR

Table 2. Relevant maternal medical history during pregnancy

Relevant maternal medical history	n (%)
Chronic arterial hypertension	20 (45.5%)
Drug addiction	9 (20.5%)
Human immunodeficiency virus infection	3 (6.8%)
Hereditary thrombophilia	3 (6.8%)
Epilepsy	3 (6.8%)
Type 1 diabetes mellitus	2 (4.5%)
Type 2 diabetes mellitus	1 (2.2%)
Chronic alcoholism	1 (2.2%)
Systemic lupus erythematosus	1 (2.2%)
Steinert myotonic dystrophy	1 (2.2%)
	44

decreased 24% during the period of the study, which ranged from 6.3% in 1992 and 4.8% in 2020 (Fig. 1). This reduction was mainly related to a decrease in early neonatal and late neonatal mortality (p < 0.001 and p = 0.003 respectively), once post-neonatal mortality remained stable over the years (p = 0.6).

The most prevalent causes of death (Table 3) were complications of prematurity (154 cases; 40%), infection (93 cases; 24%), congenital anomalies (64 cases; 16%) and perinatal asphyxia (47 cases; 12%). In four cases, the cause of death was undetermined. Of the NB who died due to congenital anomalies, 50 (78%) had no prenatal diagnosis (PND), and of these, the majority (86%; n = 43) occurred in the first 15 years of the study. The most prevalent conditions associated with early neonatal death were complications of prematurity (40%; 78/195) and perinatal asphyxia (18%; 35/195). In the group of late neonatal death, the most prevalent causes of death were complications of prematurity (44%; 67/153) and infection (29%; 44/153). In the post-neonatal mortality group, infection (45%; 19/42) was the main cause of death. Congenital anomalies and complications of prematurity were the second main causes (21%; 9/42).

At a lower GA and BW, complications of prematurity and infections were more frequent. As GA and BW increased, perinatal asphyxia and congenital anomalies become the most common causes of death.

Over the years of study, there was a decrease in the proportion of congenital anomalies related deaths (p = 0.04), mainly due to the decrease in congenital

heart disease deaths (p = 0.03). On the other hand, there was an increase in the proportion of deaths due to infection (p = 0.01). The proportion of deaths from complications of prematurity and perinatal asphyxia remained stable (Fig. 2).

Clinical and pathological concordance

Autopsy was performed in 176 NB (45%). The annual rate of autopsies ranged from 10% in 2005 to 75% in 2010. A higher rate of autopsies was performed in term NB compared to premature NB (52% and 32% respectively; p < 0.001) and in NB with higher BW (58% in BW > 2500g and 42% in BW ≤ 2500g; p = 0.01). Of the 176 autopsies performed, the pathology report was available in 118 cases. Applying the modified Goldman Classification[12], a clinical and pathological concordance was found in 91 cases (77%). Additional findings were identified in 27 (23%) autopsies (Table 4).

Discussion

In recent years, there has been a global reduction in the neonatal MR. In Europe, between 1970 and 2014, there was a reduction from 13.2 to 2.4 deaths per 1000 births[13]. A Swiz study performed between 1997 and 2006 identified a MR of 2.3% with complications of prematurity accounting for 78% of deaths (including 3499 NB)[14]. Hagen, et al.[15] conducted a study at a NICU in Norway comparing data on neonatal mortality in two different periods (1987-1988 and 1997-1998, including 1473 and 1705 NB, respectively) and found a reduction in neonatal mortality from 6.9% to 3.4%[15]. Two studies have been published in Portugal but with differences to our study as explained below[8-9]. The first study identified a 5.7% MR in a population of 1938 NB admitted between 2004-2008. The main causes of death were congenital anomalies (50%), prematurity complications (33.6%) and infections (4.5%). The second study (4026 admissions) analyses the following decade (2008-2018) and found a reduction in the MR to 3.9%.

The present study adds a longer period of analysis, during three different decades, offering more extensive data from a more representative neonatal population. The reduction in the MR shows similarities with what has been observed in other studies performed in Portugal and other European countries[8,9,13,16,17]. It reflects the progress achieved in pregnancy, childbirth and NB care. The increased use of prenatal corticosteroids, as evidenced in this study, is currently considered to be one of the interventions with greatest impact on the improvement of prognosis and survival of preterm NB[18-20].
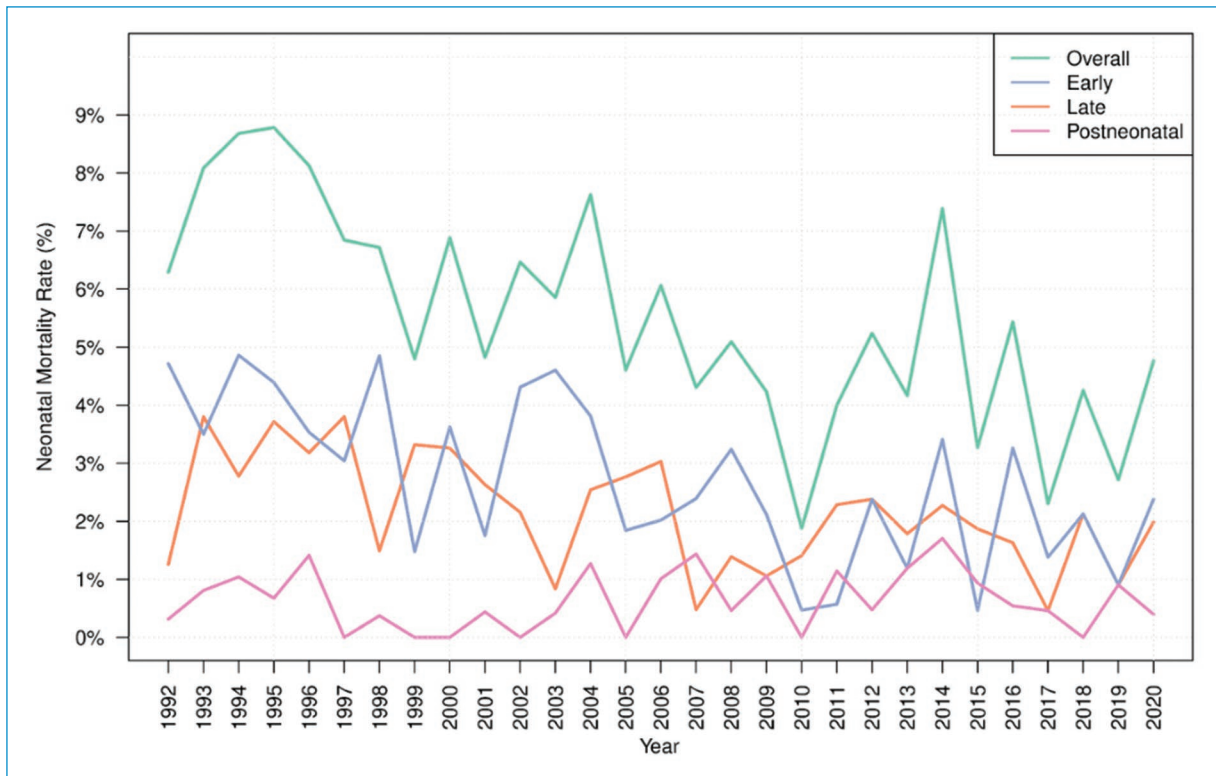
Figure 1. Evolution of the mortality rate between 1992 and 2020.

The unchanged post-neonatal MR suggests that, in some patients, death was only delayed. This highlights the need to reflect on the limitation or suspension of invasive and life-supporting measures in some cases[6,14].

As expected, most deaths occurred in NB with lower gestational age and lower BW. As regards the causes of death, there was a predominance of deaths due to complications of prematurity and infection. Comparing our results with those of the study of Costa S. et al.[8] we found a similar MR (5.6% between 2004 and 2008), but a lower number of deaths due to congenital anomalies (11.6%) and a higher number due to infections (38%) in the same period. However, the population of the previous study had a median GA of 34 weeks, which contrasts with the 29 weeks in the present study. Preterm NBs are a particularly vulnerable group to infection due to their immunological immaturity, longer hospital stay, frequent exposure to invasive procedures, and nonspecific clinical symptoms that may delay the beginning of treatment. Therefore, the higher percentage of deaths due to infection can be mainly related to a higher number of immature NBs included in the present study. The emergence of multidrug-resistant strains in the last decade may also play a role in this predominance of infection as a cause of mortality in recent years.

A previous study conducted in our NICU, which analysed the infection by multidrug-resistant bacteria between 2008 and 2017 and included 64 infectious episodes, identified a case fatality rate of 10.9% for these infections, which was higher than the value of 7% identified for healthcare-associated infections[21].

In our study, most deaths due to congenital anomalies without PND occurred in the first 15 years. Besides that, we observed a decrease in the proportion of deaths due to congenital anomalies during the period of the study. This reflects the improvement of ultrasound diagnosis and quality of PND in the last decades and justifies the fact that most deaths due to undiagnosed congenital anomalies occurred in the first years of study. Furthermore, the improvement in prenatal diagnostic acuity has also led to the termination of many pregnancies whose fetus presented severe anomalies incompatible with life.

The importance of autopsy in NICUs has been analysed in recent years, with performance rates ranging between 39% and 82%[22]. In the current study, autopsy was performed in 45% of patients, with a higher prevalence in those with higher GA and BW. These are important factors in the final decision to request a pathological examination[23]; often reserved for cases of

Table 3. Distribution of causes of death in newborns according to adaptation of the Wigglesworth classification

Classification	n (%)	Cause of death	n (%)
Complications of prematurity	154 (39.5%)	Extreme immaturity	58 (14.9%)
		Necrotizing enterocolitis	45 (11.5%)
		CNS hemorrhage	29 (7.4%)
		Pulmonary hemorrhage	21 (5.4%)
		Spontaneous intestinal perforation	1 (0.2%)
Infection	93 (23.8%)	Late-onset neonatal sepsis	44 (11.3%)
		Early-onset neonatal sepsis	19 (4.9%)
		Sepsis with meningitis	8 (2.0%)
		Sepsis with pneumonia	6 (1.5%)
		Ventilator-associated pneumonia	5 (1.3%)
		TORCH infection	4 (1.0%)
		Endocarditis	4 (1.0%)
		Pneumonia	2 (0.5%)
		Meningitis	1 (0.2%)
Congenital anomalies	64 (16.4%)	Polymalformative syndrome	15 (3.8%)
		Cardiovascular disease	14 (3.6%)
		Chromosomal anomaly	10 (2.6%)
		Musculoskeletal system disease	9 (2.3%)
		CNS disease	8 (2.0%)
		Respiratory tract disease	4 (1.0%)
		Digestive tract disease	2 (0.5%)
		Urinary tract disease	2 (0.5%)
Perinatal asphyxia	47 (12.0%)		47 (12.0%)
Other causes	32 (8.2%)	Meconium aspiration syndrome	8 (2.0%)
		Pulmonary hypertension	5 (1.3%)
		Pneumotorax	3 (0.7%)
		Disseminated intravascular coagulation	2 (0.5%)
		Hemoperitoneum	2 (0.5%)
		Metabolic disease	2 (0.5%)
		Hydrops fetalis	2 (0.5%)
		Unknown cause	4 (1.0%)
		Others	4 (1.0%)
			390

CNS: central nervous system.

"unexpected" death, in which the classic risk factor arising from the immaturity of the NB is not present. Despite clinical and pathological agreement in 77% of cases, additional findings in 23% of autopsies demonstrates its importance in clarification of the cause of death. This offers the possibility of genetic counselling

| Year	Total Deaths	Infections		Congenital Anomalies		Complications of Prematurity		Perinatal Asphyxia		Others	
	n	n	%	n	%	n	%	n	%	n	%
1992	20	3	15	2	10	6	30	3	15	6	30
1993	30	6	20	5	17	13	43	3	10	3	10
1994	25	6	24	4	16	9	36	5	20	1	4
1995	26	5	19	6	23	12	46	3	12	0	0
1996	23	3	13	5	22	10	43	3	13	2	9
1997	18	3	17	4	22	9	50	2	11	0	0
1998	18	3	17	4	22	6	33	3	17	2	11
1999	13	5	38	3	23	2	15	2	15	1	8
2000	19	4	21	4	21	9	47	2	11	0	0
2001	11	1	9	5	45	5	45	0	0	0	0
2002	15	1	7	2	13	4	27	5	33	3	20
2003	14	4	29	1	7	6	43	3	21	0	0
2004	18	6	33	2	11	8	44	1	6	1	6
2005	10	4	40	1	10	3	30	1	10	1	10
2006	12	5	42	1	8	6	50	0	0	0	0
2007	9	5	56	1	11	1	11	2	22	0	0
2008	11	3	27	2	18	5	45	1	9	0	0
2009	8	0	0	4	50	2	25	1	13	1	13
2010	4	0	0	2	50	1	25	0	0	1	25
2011	7	1	14	0	0	5	71	1	14	0	0
2012	11	3	27	1	9	5	45	2	18	0	0
2013	7	1	14	3	43	1	14	1	14	1	14
2014	13	1	8	1	8	8	62	1	8	2	15
2015	7	1	14	0	0	4	57	1	14	1	14
2016	10	4	40	0	0	4	40	0	0	2	20
2017	5	2	40	0	0	3	60	0	0	0	0
2018	8	4	50	0	0	3	38	0	0	1	13
2019	6	4	67	0	0	0	0	0	0	2	33
2020	12	5	42	1	8	4	33	1	8	1	8
p–value (χ^2)			0.01		0.04		0.99		0.11		0.56
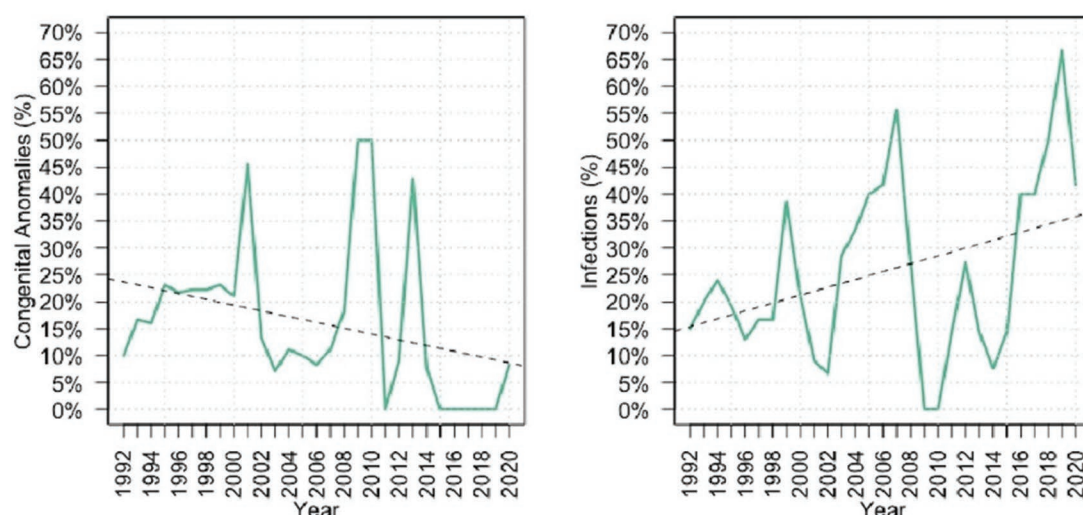
Figure 2. Distribution and trend of causes of death from 1992 to 2020.

Table 4. Additional findings identified in autopsies according to modified Goldman classification

Class	Additional findings identified in autopsies	n (%)
IA	Congenital heart disease	1 (3.7%)
	Sepsis with endocarditis	1 (3.7%)
	Constrictive pericarditis	1 (3.7%)
IB	Hereditary disease of metabolism (glycogenosis)	1 (3.7%)
IIA	Multiple organ thrombosis and ischemic changes in immediate postoperative period of intestinal atresia	1 (3.7%)
IIB	Congenital pneumonia	3 (11.1%)
	Hypoxia with multi-systemic repercussion	2 (7.4%)
	Heart and respiratory failure secondary to fetal anaemia	1 (3.7%)
III	CNS hemorrhage	10 (37%)
	Pulmonary hemorrhage	2 (7.4%)
	Hemoperitoneum	2 (7.4%)
IV	Hepatic subcapsular hematoma	1 (3.7%)
	Bilateral pulmonary lymphangiectasia	1 (3.7%)
		27

CNS: central nervous system.

and supplies important data for future approach to other patients.

The main limitations of our study are the retrospective design, which required reliance on review of medical records for details of care and the fact that it was performed in a single center, which makes it difficult to generalize the results.

Conclusion

The evolution of neonatal mortality in this NICU over three decades reflects the improvement in PND and maternal-fetal interventions. It also reflects the improvement of differentiated postnatal care, scientific, technical, and technological advances. Analysis of neonatal mortality has the potential to enable a refined clinical practice. The present study offers a reality of a single NICU, but with a long period of study, with data from immature NB. Besides the path achieved similar to other NICUs, it stands out that infection and post-neonatal mortality deserve our concern in the future. MR interpretation and comparison between NICUs are important for evolution of knowledge and care of NB. Multidisciplinary morbidity and mortality meetings can enhance the multidisciplinary communication and supports NICUs to achieve and maintain high standards of care[24].

Observations

Study presented as Oral Communication at the 49th Portuguese Congress of Neonatology, which took place on 8 and 9 April 2021.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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Gender dysphoria/gender incongruence of pre or post-pubertal onset: differences in psychiatric comorbidities and socio-familial determinants. A cross-sectional study

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Abstract

Introduction: The increase in the number of adolescents referred to specialized gender identity clinics generated an international phenomenon, that has also been experienced at the Outpatient Adolescence Service of Departamento de Pedopsiquiatria e Saúde Mental da Infância e Adolescência, Centro Hospitalar Universitário do Porto. **Objective:** To assess whether there are differences in psychiatric co-morbidities and other socio-familial determinants in pre- or post-pubertal-onset of Gender Dysphoria/Gender Incongruence. **Methods:** Selection of a convenience sample of adolescents assessed for Gender Dysphoria/Gender Incongruity at the Outpatient Adolescence Service of Departamento de Pedopsiquiatria e Saúde Mental da Infância e Adolescência, Centro Hospitalar Universitário do Porto, from January 2018 to December 2021 that was divided into two groups: pre- and post-pubertal onset. Data were analyzed with SPSS, version 26. **Results:** Forty-one adolescents with cross-gender behaviors, 28 (68.3%) females, and 13 (31.7%) males were included. Pre-pubertal cross-gender behavior was observed in 21 (51.2%) adolescents. The prevalence of psychiatric co-morbidities was 65.9% and the prevalence of social-family risk factors was 63.4%, without statistical significant differences between the two subgroups. **Discussion:** The small sample is an important limitation. Even so, results are in line with the literature, concerning the increasing number of birth-designated females presenting for care. However, there were no differences in this sample, so it is not possible to infer differences between the two subgroups regarding the compared parameters. We consider essential further studies to better understand this phenomenon and its particularities at a stage of development that is in itself turbulent.

Keywords: Adolescent. Gender incongruence. Gender dysphoria. Puberty.

Disforia de género/incongruência de género de início pré ou pós-pubertário: diferenças nas comorbilidades psiquiátricas e outros determinantes sócio-familiares. Um estudo transversal

Resumo

Introdução: O aumento do número de adolescentes encaminhados para clínicas/programas especializados em "Identidade de Género" fez desta problemática, um fenómeno mundial. O aumento de casos tem sido experienciado, também no Serviço

de Adolescentes do Departamento de Psiquiatria e Saúde Mental da Infância e da Adolescência, Centro Hospitalar Universitário do Porto. **Objetivo:** Avaliar se existem diferenças nas comorbilidades psiquiátricas e outros determinantes sociofamiliares na Disforia de género/Incongruência de género de início pré ou pós- pubertário. **Métodos:** Foi selecionada uma amostra de adolescentes avaliados em consulta de Pedopsiquiatria por Incongruência/Disforia de Género no Departamento de Pedopsiquiatria e Saúde Mental da Infância e Adolescência, Centro Hospitalar Universitário do Porto, entre janeiro de 2018 e dezembro de 202. Esta amostra foi dividida em dois subgrupos: início pré e pós-pubertário. Os dados foram submetidos a análise estatística com o programa SPSS (versão 26). **Resultados:** 41 adolescentes com comportamentos de género cruzado em que 28 (68,3%) eram do sexo feminino e 13 (31,7%) do sexo masculino. Comportamentos pré-púberes de género cruzado foram observados em 21 (51,2%) adolescentes. A prevalência de comorbilidades psiquiátricas foi de 65,9% e a prevalência de fatores de risco sociofamiliares foi de 63,4%, sem diferenças estatisticamente significativas entre os 2 subgrupos. Dados analisados com SPSS, versão 26. **Discussão:** Uma limitação importante deste estudo é o pequeno tamanho da amostra. Mesmo assim, os resultados estão de acordo com o que vem sendo descrito na literatura, no que diz respeito ao crescente número de mulheres que se apresentam com esta problemática. Apesar disso, não foram encontradas diferenças estatisticamente significativas nos subgrupos, pré- e pós-pubertário, pelo que não é possível inferir acerca das diferenças nas comorbilidades psiquiátricas e outros determinantes sócio-familiares. Consideramos necessário e imprescindível a realização de mais estudos para melhor compreender este fenómeno e as suas particularidades numa fase de desenvolvimento por si turbulenta.

Palavras-chave: Adolescente. Incongruência de género. Disporia de género. Puberdade.

Keypoints

What is known

– There has been a progressive de-pathologization of gender diversity issues, and the disease classification manuals used in mental health have been in line with this trend.

– At some point in childhood, many children experiment with gender expression and roles, and in some children cross-gender behavior and expressions are more consistent, persistent, and insistent than iamong peers.

– Trans adolescents have higher rates of depression, suicidal behavior, and self-harm, as well as eating disorders.

What is added

– We found a high percentage of adolescents who present with GD/GI in the absence of manifestations of GD/IG in childhood.

– No differences were found between pre- and post-pubertal GD/GI of pre- or post-pubertal onset.

– Facing the unpredictability of DG/GI evolution, gender questioning, and gender role explorations along the other developmental tasks, the authors suggests that a non-binary or gender fluid identity may be more suitable for some adolescents.

Introduction

Exploring gender and sexual behaviors is a normal part of child development[1-7].

Gender identity is the subjective notion that someone has of themselves as being male or female, without this being dependent on the genitalia or sex chromosomes they present[8-10]. The construction of this dimension takes place progressively along the psychological and sexual development of each person. It is important to emphasize that gender identity is not a dichotomous/binary conceptualization (male vs. female), as it was thought in the past, but a dimensional concept (continuum between female and male)[11-18].

Over the past several years, there has been an increasing number of adolescents referred to specialized gender identity clinics/programs, which made this an international phenomenon. Alongside this increase, there has been a progressive de-pathologization of gender diversity issues, and the disease classification manuals used in mental health have been in line with this trend, changing the terminology. Currently, gender dysphoria (GD) has replaced Gender Identity Disorder in the DSM-5, emphasizing the malaise and suffering experienced by the marked incongruity of gender and assigned sex. ICD-11 introduces the terminology of Gender Incongruence (GI) in Childhood and Adolescence and no longer considers GI a mental disorder by eliminating it from the chapter of mental disorders[19-26].

It has long been known that there are at least two developmental pathways that lead to GD. In early-onset gender dysphoria, the signs and symptoms are apparent from an early age (e.g., the preschool years, if not even a bit earlier). In late-onset gender dysphoria, the signs and symptoms do not appear until puberty, if not later. In recent years, clinicians have seen an ever-increasing number of post-puberty cases of GD in

birth-assigned females with rapid-onset clinical manifestations[14], termed "rapid-onset gender dysphoria" (ROGD)[12,27-31].

Literature suggests that in comparison to their peers, trans adolescents have higher rates of depression, suicidal behavior, and self-harm, as well as eating disorders[14].

Despite the increasing numbers of adolescents seeking gender reassignment treatment, scientific knowledge is still very scarce[20,32,33]. So, with this work the authors intend to characterize the population of adolescents seeking GD treatment at the Adolescence Outpatient Service of Departamento de Pedopsiquiatria e Saúde Mental da Infância e Adolescência, Centro Hospitalar Universitário does Porto (DPSMIA, CHUPorto) and compare the GD of pre-pubertal onset with that of post-pubertal onset, regarding co-morbidities and other socio-familial determinants.

Methods

A retrospective and longitudinal study was developed at the Adolescence Outpatient Service of DPSMIA, CHUPorto, which serves patients with psychiatric illness, from 12 to 18 years of age. All adolescents referred and assessed for gender incongruence or dysphoria from January 2018 to December 2021 were included in the study. Based on empirical conclusions, the authors established the following hypotheses:

– Psychiatric co-morbidities are more frequent in adolescents with prepubertal GD.
– Social and familiar risk factors have a greater impact on prepubertal gender dysphoria.

To study these research hypotheses, the clinical files of users were consulted and the following data were recorded:

– Age at referral date.
– Gender assigned at birth.
– Age of menarche.
– Age of appearance of cross-gender interests and/or behaviors: prepubertal or postpubertal.
– Previous psychiatric care (not related to gender issues).
– Psychiatric co-morbidities: social anxiety disorder, depressive disorder, non-suicidal self-injury (NSSI), Attention Deficit Hyperactivity Disorder (ADHD), Eating Behavior Disorder (EBD), conduct disorder, autism spectrum disorder (ASD), other anxiety disorders, substance use disorder, other childhood emotional disorders, no psychopathology.
– Socio-family risk factors: history of sexual abuse, maltreatment, neglect, immigration and age at the time of immigration, integration in the peer group, history of bullying, intra-family violence, parental detention, parental psychopathology.
– Type of family (nuclear, extended, single-parent, reconstructed, institutionalized).

The project was approved by the ethical committee of our institution. All the information was anonymous and confidential.

Statistical analysis

Data were analyzed with SPSS, version 26. Descriptive statistics were presented as frequencies (n) and percentages (%) for categorical variables, means (M), and standard deviations (SD) for continuous variables with symmetrical distributions. Univariate logistic regressions were implemented to assess the associations with pre-pubertal cross-gender behavior. Chi-square tests and Pearson correlations were used to assess sample differences. Odds Ratios (OR) were estimated as effect size. Adjusted ORs were not estimated because due to the results no multivariate logistic regressions were implemented. Significance was considered for $p < 0.05$ and marginal significance for $p < 0.10$.

Results

A total of 41 adolescents with cross-gender behaviors were assessed for gender incongruence/dysphoria in our department, 28 (68.3%) females and 13 males (31.7%) were included in this study. Pre-pubertal cross-gender behavior was observed in 21 (51.2%) of adolescents. We also noticed an increasing number of post-pubertal cross-gender behavior after the COVID-19 Pandemic, however this was not an aim of our study. Previous psychiatric care was present in 18 (43.9%) adolescents. The prevalence of psychiatric co-morbidities was 65.9% and the prevalence of social-family risk factors was 63.4%. The family type was nuclear (n = 21, 51.2%) and non-nuclear (n = 20, 48.8%). The mean age at referral was 15.12 (SD = 1.44), ranging from 10 to 17 years old. The mean age at the onset of cross-gender behavior was 8.70 (SD = 4.82), with a minimum of 2 and a maximum of 16 years old. The mean age at menarche for females was 11.36 (SD = 1.19), ranging from 8 to 14 years old. Seven adolescents in this sample were immigrant. The mean years of immigration were 12.38 (SD = 0.77), ranging from 8 to 14 years (Table 1). As described in the table, psychiatric co-morbidities were found in 27 cases, with more than 1 in 3 cases. Thus, the presence of depressive disorders was observed in

Table 1. Sample characteristics

	Descriptive statistic

Gender at birth
  Female
  Male
	
	28 (68.3%)
	13 (31.7%)

Pre-pubertal cross-gender behavior
  No
  Yes
	
	20 (48.8%)
	21 (51.2%)

Previous psychiatric care
  No
  Yes
	
	23 (56.1%)
	18 (43.9%)

Psychiatric co-morbidities
  No
  Yes
	
	14 (23.1%)
	27 (65.9%)

Social-family risk factors
  No
  Yes
	
	15 (36.6%)
	26 (63.4%)

Type of family
  Nuclear
  Non-nuclear
  Age at referral (n = 41)
  Age at menarche (28 females)
  Age at onset of cross-gender behavior (n = 41)
  Age at the time of immigration (n = 7)
	
	21 (51.2%)
	20 (48.8%)
	15.12 (1.44) [10-17]
	11.36 (1.19) [8-14]
	8.70 (4.82) [2-16]
	10.71 (2.36) [8-14]

Table 2. Results for univariate and multivariate logistic regressions considering pre-pubertal cross-gender behavior as outcome

	Pre-pubertal cross-gender behavior		Univariate		Multivariate		
	No (n = 20)	Yes (n = 21)	OR	p-value	aOR	p-value	95% CI

Gender at birth
  Female
  Male
	
	15 (75.0%)
	5 (25.0%)
		
		13 (61.9%)
		8 (38.1%)
			
			1
			1.85
				
				1
				0.370
					
					-
					-
						
						-
						-
							
							-
							-

Previous psychiatric care
  No
  Yes
	
	12 (60.0%)
	8 (40.0%)
		
		11 (52.4%)
		10 (47.6%)
			
			1
			1.36
				
				1
				0.624
					
					-
					-
						
						-
						-
							
							-
							-

Psychiatric co-morbidities
  No
  Yes
	
	7 (35.0%)
	13 (65.0%)
		
		7 (33.3%)
		14 (66.7%)
			
			1
			1.08
				
				1
				0.910
					
					-
					-
						
						-
						-
							
							-
							-

Social-family risk factors
  No
  Yes
	
	7 (35.0%)
	13 (65.0%)
		
		8 (38.1%)
		13 (61.9%)
			
			1
			0.88
				
				1
				0.837
					
					-
					-
						
						-
						-
							
							-
							-

Type of family
  Nuclear
  Non-nuclear
  Age at referral
  Age at menarche
	
	11 (55.0%)
	9 (45.0%)
	15.10 (1.38)
	11.35 (1.18)
		
		10 (47.6%)
		11 (52.4%)
		15.14 (1.53)
		12.00 (1.10)
			
			1
			1.34
			1.02
			1.76
				
				1
				0.637
				0.923
				0.096
					
					-
					-
					-
					-
						
						-
						-
						-
						-
							
							-
							-
							-
							-

9, as well as ADHD, anxiety disorders in 8, self-injurious behaviors in 5, conduct disorder in 1, and school refusal in 1. Socio-family risk factors were found in 26 cases, with more than one risk factor being found in 6 of the 26 cases. Thus, the presence of poor integration in the peer group was observed in 13, intra-family violence in 10, immigration in 7, and institutionalization in 1 case. When we divided the sample considering pre-pubertal

cross-gender behaviour, we conclude that there were not statistical diferences in both groups regarding psychiatric co-morbidities and social-family risk factors (Table 2).

Discussion

The prevalence of GD is hampered by the social stigma of gender diversity and lack of a standardized definition, but we do not doubt that adolescent referrals for GD/GI are increasing internationally, and our department is no exception. The growing social acceptance, wider access to information, and opportunities for contact through social media have played a role in this process[19,20,34,35]. There are several factors that support the idea of social and peer contagion for a type of adolescent-onset or late-onset gender dysphoria. Firstly, there is an increasing number of friends within peer groups who identify as transgender. Secondly, there seems to be a pattern of outbreaks of transgender identification within these peer groups. Additionally, a significant percentage of peer groups have a majority of members identifying as transgender. Finally, the dynamics of peer groups observed also contribute to the plausibility of social and peer contagion as a factor in the development of this type of gender dysphoria.

In these cases, the development of gender dysphoria begins suddenly during or after puberty in an adolescent or young adult who would not have met criteria for gender dysphoria in childhood[36-38]. Since the 2000s, several gender identity services for minors across western countries have reported an increase in referrals, and several studies suggest that the average age of the first visit to a specialist is becoming lower. Simultaneously, the earlier overrepresentation of birth-assigned males was equaled or turned to an overrepresentation of birth-assigned females, suggesting strong generalizability[39].

Although the small sample of this study is an important limitation, we can assume that the clear majority of birth-designated females presenting for care is in line with what has been described in the literature. Chi-square tests and Pearson correlations were used to assess sample differences. which were not found, so it is not possible to infer differences between the two subgroups regarding the compared parameters (unconfirmed hypotheses).

In our study we found an almost equal number of adolescents with prepubertal GD (inferred by the report of prepubertal cross gender behavior) and postpubertal GD. It is described that early onset GD during childhood is more frequent in males at birth, while later

onset during adolescence is more frequent in girls at birth[12,14]. In our study, a higher percentage of females assigned at birth was found in the postpubertal group (75% versus 61.9%) although without statistical significance, which may be related to the sample size. There has recently been described an increasing number of postpubertal cases of birth-assigned females with gender incongruence/dysphoria with rapid onset clinical manifestations, without having a history of gender variance during childhood, a phenomenon described as "rapid-onset gender dysphoria[12,14]. This is in line with our findings of more postpubertal cases of GD in birth-assigned females. Concerning the main goal of this study, no differences were found between Gender Dysphoria/Gender Incongruence of pre- or post-pubertal onset regarding psychiatric co-morbidities (65% versus 66.7%) and social family factors. In our study population the prevalence of psychiatric co-morbidities was 65.9% and the prevalence of social-family risk factors was 65.7%, with emphasis on poor integration in the peer group and intra-family violence.

Based on a variety of measurement approaches, it has been found that adolescents referred for GD have more behavioral and emotional problems than non-clinical adolescent samples, but are more similar when compared to adolescents referred for other mental health concerns[39,40]. Descriptive studies of adolescents referred to specialized gender identity services at different centers in Europe and North America have mainly suggested that 40-45% of them present with clinically significant psychopathology[17,39,41]. One of the explanations for the elevated rate is that GD has emerged as secondary to another, more "primary" mental health, such as autism spectrum disorder or borderline personality disorder, or as a result of severe trauma (sexual abuse). Another explanation is that GD is inherently distressing, which leads to clinical symptoms such as anxiety or depression[42]. The most common explanation is that the co-occurring mental health issues are simply secondary to factors such as family rejection or social ostracism within the peer group[43-48]. In our study, the prevalence of psychiatric co-morbidities was 65.9%, with emphasis on depressive and anxiety behaviors, ADHD, and self-harm. Only one case of conduct disorder was reported and there was no case of ASD. Except for the absence of ASD, these results are in line with international studies that show that the most reported disorders are depression and anxiety disorders with self-harm and suicidal ideation/behavior also common, whereas conduct disorder and antisocial development do not appear common in this population[12]. Likewise, community-level information suggests

that transgender-identifying youths present four to six times more often with depression and three to four times more often with self-harm and/or suicidal behavior compared with cisgender adolescents[49-55].

In our knowledge, this is the first article that characterized the population referred to and assessed at the department by DG/IG and compared the GD of pre-pubertal onset with that of post-pubertal onset, regarding co-morbidities and other socio-familial determinants. Despite the small sample, we consider that this is a relevant study, as it reveals the reality of our department, showing some similarities with what has been described in the literature.

Although we cannot predict the evolution of DG/GI in pediatric age, this work emphasizes the high percentage (almost half) of adolescents who present with GD/GI in the absence of manifestations of GD/IG in childhood. Because of this unpredictable evolution, at pediatric age, the diagnosis must be carefully established.

At Adolescent Outpatient Service of DPSMIA, CHUPorto we consider that, in some dubious cases, gender identity issues may be, after all, an identity crisis, in which the gender questioning and gender role exploration go along with the exploration of other identity issues. A non-binary transgender identity may be more suitable for some of these adolescents, given the possibility of some fluidity in gender identity. And that's why we as mental health professionals adopt the non-binary gender conceptualization.

This is a specific and unique phenomenon, that can be difficult for clinicians to stay current with guidelines in a rapidly changing field and, as a consequence, poses numerous challenges in terms of diagnoses and therapy. That's why we consider it necessary to carry out further studies to better understand this phenomenon and its particularities at a stage of development that is turbulent, per se.

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Impact of early discharge on the newborn

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Abstract

Introduction and objectives: In Western countries, the average length of stay in the postpartum period for newborns without complications follows a decreasing trend. The aim of the present study was to evaluate the impact of early discharge on the newborn, particularly regarding the risk of hospital readmission. **Methods:** Cross-sectional study of newborns with early discharge born in a level II hospital with differentiated perinatal support, between June 2021 and May 2022. Clinical and demographic data were obtained from the analysis of the patient's medical records and phone contact. Early discharge was considered to be the interval less than or equal to 48h between birth and discharge of the newborn. **Results:** From the 508 newborns enrolled in our study, 217 (42.7%) had an early discharge and 291 (57.3%) had a standard length of stay. The mean length of stay was 2.3 days (1.8 early discharge vs 2.6 discharge after 48h). In the comparative analysis (early discharge vs. discharge after 48h) there was no statistically significant association between early discharge and hospital readmission rate (0.5% vs 1.4%, p = 0.399), emergency observation rate (13.4% vs 10%, p = 0.233) or abandonment of exclusive breastfeeding within 15-days after postpartum discharge (22.7% vs 28.4%, p = 0.180). The results were similar for the subgroup of NB discharged within 39h. Instrumented delivery, birth weight less than 2500g, prematurity and phototherapy were factors that contributed to longer length of stay. **Conclusion:** In this study, early discharge was not associated with a higher risk for the newborn. Regarding the clinical and social advantages, this approach should be considered and supported by adequate surveillance in primary health care.

Keywords: Newborn. Early discharge. Hospital readmission. Breastfeeding.

Impacto da alta precoce no recém-nascido

Resumo

Introdução e objetivos: Nos países ocidentais, a média de dias de internamento do recém-nascido (RN) no pós-parto sem complicações percorre uma tendência decrescente. O objetivo do presente estudo foi avaliar o impacto da alta precoce no RN, em particular quanto ao risco de readmissão hospitalar. **Métodos:** Estudo transversal, realizado num hospital de nível II com apoio perinatal diferenciado. Incluíram-se RN admitidos entre junho 2021 e maio 2022. Os dados foram obtidos através da análise dos processos clínicos e contacto telefónico. Considerou-se a definição consensualizada de alta precoce o internamento com intervalo inferior ou igual a 48 horas. **Resultados:** Foram incluídos 508 RN, 217 (42,7%) tiveram alta precoce e 291 (57,2%) após as 48 horas. A média de internamento foi 2,3 dias (1,8 alta precoce *vs* 2,6 alta após 48h). Na análise

compratival (alta precoce *vs* alta após 48h) não se verificou associação estatisticamente significativa da alta precoce com a taxa de readmissão hospitalar (0,5% *vs* 1,4%, p = 0,399), a taxa de observação em urgência (13,4% *vs* 10%, p = 0,233) ou o abandono do aleitamento materno exclusivo nos 15 dias após a alta (22,7% *vs* 28,4%, p = 0,180). Os resultados foram sobreponíveis para o subgrupo com alta antes das 39h. O parto instrumentado, peso ao nascimento inferior a 2500g, prematuridade e fototerapia foram fatores que contribuíram para maior tempo de internamento. **Conclusão:** Neste estudo, a alta precoce não se associou a maior risco para o RN. Perante a perspetiva de vantagens clínicas e sociais, esta abordagem deverá ser ponderada e suportada por uma vigilância adequada em ambulatório.

Palavras-chave: Recém-nascido. Alta precoce. Readmissão hospitalar. Aleitamento materno.

Keypoints

What is known
- In recent years, in Western countries, there has been a downward trend in the average length of stay in the postpartum period for newborns.
- Earlier discharge of mothers and their babies has potential advantages.
- The existing evidence does not allow to recommend or contraindicate early discharge.

What is added
- A lower probability of early discharge was associated with cesarean delivery; assisted vaginal delivery; birth weight < 2500g; gestational age < 37 weeks and the need for phototherapy. Thus, these factors should be considered when the newborn is discharged, as they are well-established risk factors for readmission.
- In this study, early discharge was not associated with a higher rate of readmission, higher rate of abandonment of exclusive breastfeeding or higher rate of observation in an emergency context in the 15-day period after discharge.
- The mother-newborn dyad and its competences must be considered when proposing discharge.

Introduction

Early discharge is defined, according to the American Academy of Pediatrics, as the interval less than or equal to 48 hours between birth and discharge of the newborn[1]. However, clinical practice implemented in each country is variable and early discharge can vary from 12 to 72 hours after birth. In 2018, the average length of stay was 4.9 days in Hungary, 3.9 days in France, 3.6 days in Austria, 2.3 days in Sweden and 1.4 days in United Kingdom[2].

Early discharge is associated with benefits such as the promotion of family relationships, contributing to greater involvement of the father and siblings in caring for the newborn, improvement in the quality of maternal rest and sleep, reduced exposure to nosocomial infections to the mother-newborn dyad, and reduced costs associated with hospital admissions[3,4,5].

In recent years, there has been a downward trend in the average length of stay in the postpartum period for newborns without complications in Western countries. The European average number of days of postpartum hospitalization has decreased from 5 days in 2000 to 3.2 days in 2014[5]. In countries such as Sweden, there has been a decrease in postpartum length of stay from 6 days in 1970 to 2.3 days in 2010, in Belgium a reduction from 4.9 days of hospitalization in 2000 to 3.7 days

in 2014[3,6,7,8]. In the particular case of the United Kingdom, where childbirth is the leading cause of hospital admission, with about 800,000 births annually and an estimated cost to the National Health Service of £2.5 billion per year[9], the need to reduce days of postpartum hospitalization while maintaining quality of care has become imperative. Midwives provide most perinatal care, typically comprising three phases: antenatal (8-10 visits), intrapartum, and postnatal. After birth, mothers and newborns are included in the directed national healthcare program, first in the hospital and then on an outpatient basis (at home or clinic), for a minimum period of 10 days, occurring between 3 to 6 visits. These aspects contribute to a further reduction of inpatient days, reduction in costs associated with hospital admission and better postnatal care[9].

Hospital readmission can be defined as admission within 30 days of discharge from the hospital. Readmissions in the first 15 days after discharge are considered early readmissions, with a higher probability of being directly related to the first hospitalization[10]. The most frequently identified conditions in newborn hospital readmission event are jaundice and weight loss (related with breastfeeding problems)[11].

Despite the above, the existing evidence does not support a recommendation in favor or against early discharge. Aspects such as adapting to breastfeeding,

clinical conditions that only manifest themselves from the second day of life and the need to teach mother to provide care for the newborn are sources of concern. These last ones can constitute disadvantages for the implementation of early discharge[5,12].

At our hospital, after birth, neonates are admitted with their mothers (rooming-in policy) if the gestational age is greater than 33 weeks, without risk factors, with an appropriate weight (usually > 1800 grams) and a stable clinical condition. This practice is achieved with safety supported by strict clinical surveillance. The outcomes are good throughout the years of practice of our NICU. The newborn-mother dyad is discharged together according to clinical stability and breastfeeding adaptation.

The present study aims to evaluate the impact of early discharge on the newborn. The intended was to assess the hospital readmission rate and its causes in the first 15 days after postpartum discharge, the need for observation in an emergency context, as well as the impact on breastfeeding and birth weight recovery.

Methods

Definitions

The following definitions were considered in the present study:

– Early discharge: interval less than or equal to 48 hours between birth and discharge of the newborn[1].

– Very early discharge: interval less than or equal to 39 hours between birth and discharge of the newborn.

– Standard length of stay: discharge 48 hours after the delivery.

– Length of stay: period from birth to discharge (in full hours).

– Readmission: newborns requiring hospitalization and hospital care within the first 15 days after postpartum discharge[10].

Study sample

During the study period, a total of 2,629 deliveries were performed in our hospital. Inclusion criteria included healthy newborns delivered at Hospital Garcia de Orta between June 2021 and May 2022 with a gestational age greater than 34 weeks and uncomplicated maternal postpartum period that did not interfere with increased length of stay of the newborn. Newborns requiring NICU admission, with gestational less than 34 weeks, respiratory distress, perinatal asphyxia, congenital malformations, poly-malformative syndromes or prolonged hospitalization due to maternal cause were excluded. Of the 2.629 deliveries, 255 newborns were excluded: 188 required admissions to the Intensive Care Unit (NICU), 63 were newborns with gestational age inferior to 34 weeks, three had a prolonged admission due to maternal cause and one refusal to participate in the study (Fig. 1). The selection of individuals to integrate the sample was carried out through simple randomization with Microsoft Excel® software. Five hundred and fifty newborns were included and 42 were lost for follow-up. The remaining 508 newborns were enrolled in our study. The discharge criterion was defined by the physician responsible for the newborn's discharge, according to the clinical criteria and practice of the unit.

Study location

The study was carried out in a Portuguese level two hospital with differentiated perinatal support between June 2021 and May 2022.

Study design

A cross-sectional study was carried out. The sample size was set to a 95% confidence interval with an absolute precision of 5%. Two groups were posterior established, one included the newborns with early discharge and the other included newborns with a standard length of stay (discharge 48 hours after the delivery).

Data collection

Data was obtained from the analysis of the patient's electronic medical records. Data analysis was carried out, including demographic data (sex, maternal age, parity, delivery mode, gestational age, birth weight), presence of jaundice and need for phototherapy, breastfeeding at hospital discharge and interval between birth and discharge in hours. Follow-up by telephone contact was performed on the 15th day after hospital discharge. Data was obtained from parent's report and medical records, especially hospital readmission and the causes for readmission, observation in an emergency context and its reasons, feeding after hospital discharge and birth weight recovery.

Statistical analysis

Statistical analysis was performed using the Fisher exact test and chi-square test to compare readmission
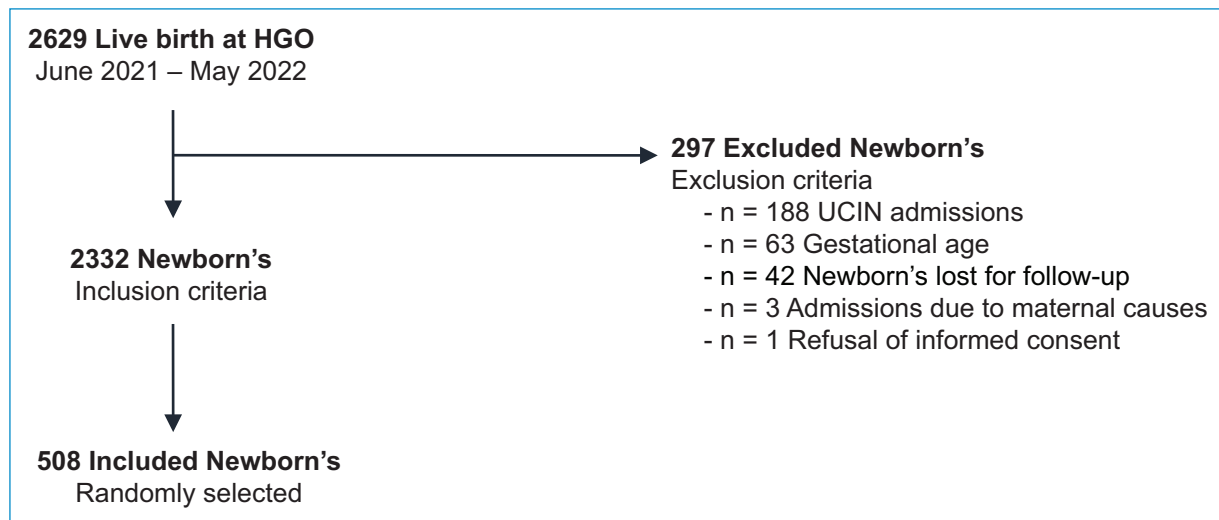
Figure 1. Study flow diagram.

rates, observation in an emergency context, breastfeeding and recovery of birth weight after discharge between groups. The chi-square test was performed to find possible associations between categorical variables. Odds ratio was calculated for the statistically significant associations and T-test for equality of means was performed to compare means of maternal age, birth weight and gestational age. The statistical work was carried out in SPSS® Statistics 28 (IBM Corp., 2021, United States of America); p values of 0.05 were considered statistically significant.

Ethical considerations

The study was approved by the hospital's Ethics Committee. Informed consent was obtained from all participants.

Results

General sample characterization (Table 1, n = 508)

The general sample included a total of 508 newborns with a median of 52 hours (30-100h) from birth to discharge. Of the 508 newborns, 255 were male and 253 were female. The median maternal age was 31 years, and 264 mothers (52%) were primiparous. The cesarean delivery rate was 30% (n = 153). The median birth weight was 3.240g, with a median gestational age of 39 weeks and five days. Twenty-five (4.9%) newborns had a gestational age of less than 37 weeks. Jaundice

was found in 299 newborns (58.9%), with 38 (7.5%) requiring phototherapy. Four hundred and thirty-five (85.6%) newborns were discharged under exclusive breastfeeding.

Early discharge group characterization (Table 1, n = 217)

The early discharge group included 217 newborns (42.7%) with a median of 43 hours (30-48h) from birth to discharge. Of the 217 newborns, 112 were male and 105 were female. The median maternal age was 31 years, and 107 mothers (49.3%) were primiparous. The cesarean delivery rate was 7.8% (n = 17). The median birth weight was 3.295g, with a median gestational age of 39 weeks and six days. Three newborns (1.4%) had a gestational age of less than 37 weeks. Jaundice was found in 123 newborns (56.7%), with two (0.9%) requiring phototherapy. At hospital discharge, 185 (85.3%) newborns were exclusively breastfed.

Standard length of stay group characterization (Table 1, n = 291)

The standard length of stay group included 291 newborns (57.3%) with a median of 60 hours (48-100h) from birth to discharge. Of the 291 newborns, 143 were male and 148 were female. The median maternal age was 31 years, and 157 mothers (54%) were primiparous. The cesarean delivery rate was 46.7% (n = 136). The median birth weight was 3.185g, with a median gestational age of 39 weeks and four days. Twenty-two

Table 1. Neonatal data - demographic characterization of the general sample, early discharge group and standard length of stay group and statistical analyses

Demographic characterization	General sample (n = 508)	Early discharge group (n = 217)	Standard length of stay group (n = 291)	Statistic significancy	Odds ratio
Gender					
Female, n (%)	253 (49.8)	105 (48.4)	148 (50.9)	p = 0.581*	N/C
Male, n (%)	255 (50.2)	112 (51.6)	143 (49.1)		
Mode of delivery					
Normal vaginal, n (%)	286 (56.3)	172 (79.3)	114 (39.2)	Reference	Reference
Caesarean section, n (%)	153 (30.1)	17 (7.8)	136 (46.7)	p < 0.001*	12.07 (95%, IC 6.92 to 21.07)
Assisted vaginal, n (%)	69 (13.6)	28 (12.9)	41 (14.1)	p < 0.005*	2.21 (95%, IC 1.29 to 3.78)
Media/median GA	39W+3D/39W+5D	39W+6D/39W+6D	39W+2D/39W+4D	p < 0.001‡	N/C
(min-max)	(35W+3D-41W+6D)	(35W+6D-41W+6D)	(35W+3D-41W+5D)		
Gestational age					
Term, n (%)	264 (52)	109 (50.2)	155 (53.3)	Reference	Reference
< 2500g, n (%)	25 (4.9)	3 (1.4)	22 (7.6)	p < 0.005*	5.16 (95%, IC 1.51 to 17.66)
Term > 40S, n (%)	219 (43.1)	105 (48.4)	114 (39.2)	p = 0.143*	N/C
Media/median birth weight (g) (min-max)	3244/3240 (1900-4679)	3327/3295 (2338-4679)	3183/3185 (1900-4640)	p < 0.001‡	N/C
Birth weight					
2500-4000g, n (%)	448 (88.2)	196 (90.3)	252 (86.6)	Reference	Reference
< 2500g, n (%)	30 (5.9)	5 (2.3)	25 (8.6)	p < 0.005*	3.89 (95%, IC 1.46 to 10.34)
> 4000g, n (%)	30 (5.9)	16 (7.4)	14 (4.8)	p = 0.306*	N/C
BW/GA					
AGA, n (%)	426 (83.9)	185 (85.3)	241 (82.8)	Reference	N/C
SGA, n (%)	64 (12.6)	22 (10.1)	42 (14.4)	p = 0.172*	
LGA, n (%)	18 (3.5)	10 (4.6)	8 (2.7)	p = 0.310*	
Jaundice					
Yes, n (%)	299 (58.9)	123 (56.7)	176 (60.5)	p = 0.389*	N/C
No, n (%)	209 (41.1)	94 (43.3)	115 (39.5)		
Phototherapy					
Yes, n (%)	38 (7.5)	2 (0.9)	36 (12.4)	p < 0.001†	15,18 (95%, IC 3.61 to 63.76)
No, n (%)	470 (92.5)	215 (99.1)	255 (87.6)		
Feeding at hospital discharge					
Breast, n (%)	435 (85.6)	185 (85.3)	250 (85.9)	p = 0.131*	N/C
Formula, n (%)	15 (3.0)	10 (4.6)	5 (1.7)		
Mixed, n (%)	58 (11.4)	22 (10.1)	36 (12.4)		
Media/median interval between birth and discharge, hours (min-max)	54/52 (30-100)	42/43 (30-48)	63/60 (49-100)	N/A	N/C

Table 2. Maternal data - demographic characterization of the general sample, early discharge group and standard length of stay group and statistical analyses

Demographic characterization	General sample (n = 508)	Early discharge group (n = 217)	Standard length of stay group (n = 291)	Statistic significance	Odds ratio
Media/median maternal age, years (min-max)	31.4/31 (16-45)	31.3/31 (16-45)	31.6/31 (18-45)	p = 0.575‡	N/C
Maternal age (years)				p = 0.425*	N/C
< 20, n (%)	10 (2)	3 (1.4)	7 (2.4)		
20-24, n (%)	56 (11)	23 (10.6)	33 (11.3)		
25-29, n (%)	125 (24.6)	54 (24.9)	71 (24.4)		
30-34, n (%)	151 (29.7)	73 (33.6)	78 (26.8)		
> 35, n (%)	166 (32.7)	64 (29.5)	102 (35.1)		
Parity				p = 0.300*	N/C
Primiparous, n (%)	264 (52)	107 (49.3)	157 (54.0)		
Multiparous, n (%)	244 (48)	110 (50.7)	134 (46.0)		

Min: minimum; max: maximum; N/A: not applicable; N/C: not calculated.
*Chi-square test.
†Fisher exact test.
‡T-test for equality of means.

(7.6%) newborns had a gestational age of less than 37 weeks. Jaundice was found in 176 newborns (60.5%), with 36 (12.4%) requiring phototherapy. At hospital discharge, 250 (85.9%) newborns were exclusively breastfed.

Characterization of the readmissions (Table 2, n = 5)

A total of five newborns (1%) were readmitted within 15 days after discharge, one from the early discharge group and four from the standard length of stay group.

In the early discharge group, the newborn was readmitted for jaundice requiring phototherapy. In the control group, the reasons for readmission were the infectious cause (n = 2), weight loss (n = 1) and feeding difficulties in the context of laryngotracheomalacia (n = 1).

Characterization of the observation in an emergency context (Table 2, n = 58)

A total of 58 newborns (11.4%) were observed in an emergency context within 15 days after discharge.

In the early discharge group, 29 (13.4%) newborns were observed in an emergency context, the reasons for observation being nasal obstruction (n = 6), neonatal conjunctivitis (n = 5), inflammatory signs of the umbilical cord (n = 4), irritability (n = 4), jaundice (n = 3), colic (n = 2), constipation (n = 2) and general caregiver concerns (n = 3).

In the standard length of stay group, 29 (10%) newborns were observed in an emergency context, the main reasons for observation being nasal obstruction

(n = 6), colic (n = 4), inflammatory signs of the umbilical cord (n = 3), irritability (n = 3), jaundice (n = 2), breast swelling (n = 2), feeding difficulties (n = 2), diaper dermatitis (n = 2), fever (n = 2), decreased urine output (n = 2) and general caregiver concerns (n = 1).

Characterization of the type of feeding after discharge and birth weight recovery (Table 2)

Fifteen days after discharge, 343 newborns (67.5%) were on exclusive breastfeeding. In the early discharge group, 149 newborns (68.7%) were exclusively breastfed and 48 (22.1%) were breastfed supplemented with infant formula. In the standard length of stay group, 194 newborns (66.7%) were exclusively breastfed and 79 (27.1%) were breastfed supplemented with infant formula.

Of the newborns who were exclusively breastfed at discharge, 113 newborns (26%) abandoned exclusive breastfeeding within 15-days after discharge, 42 (22.7%) in the early discharge group and 71 (28.4%) in the control group.

Fifteen days after discharge, 380 (77.6%) newborns regained their birth weight, 168 (80.4%) from the early discharge group and 212 (75.4%) from the control group.

Statistical analysis (Table 1, 2, 3 and 4)

A lower probability of early discharge was associated with: cesarean delivery (7.8% vs 46.3%, p value < 0.001) with an odds ratio of 12.07 (95%, IC 6.92 to 21.07); assisted vaginal delivery (12.9% vs 14.1%, p value < 0.005)

Table 3. Comparison of readmission rate, observation in an emergency context, feeding after discharge and recovery of birth weight between early discharge group and standard length of stay group

	General sample (n = 508)	Early discharge group (n = 217)	Standard length of stay group (n = 291)	Statistic significancy
Re-admission				p = 0.399*
Yes, n (%)	5 (1)	1 (0.5)	4 (1.4)	
No, n (%)	503 (99)	216 (99.5)	287 (98.6)	
Observation in an emergency context				p = 0.233†
Yes, n (%)	58 (11.4)	29 (13.4)	29 (10)	
No, n (%)	450 (88.6)	188 (86.6)	262 (90)	
Feeding after discharge				p = 0.240†
Breast, n (%)	343 (67.5)	149 (68.7)	194 (66.7)	
Formula, n (%)	38 (7.5)	20 (9.2)	18 (6.2)	
Mixed, n (%)	127 (25)	48 (22.1)	79 (27.1)	
Abandoned exclusively breastfeeding	(n = 435)	(n = 185)	(n = 250)	p = 0.180†
Yes, n (%)	113 (26)	42 (22.7)	71 (28.4)	
No, n (%)	322 (74)	143 (77.3)	179 (71.6)	
Recover birth weight	(n = 490)	(n = 209)	(n = 281)	p = 0.195†
Yes, n (%)	380 (77.6)	168 (80.4)	212 (75.4)	
No, n (%)	110 (22.4)	41 (19.6)	69 (24.6)	

*Fisher exact test.
†Chi-square test.

Table 4. Comparison of readmission rate, observation in an emergency context, feeding after discharge and recovery of birth weight between very early discharge group and standard length of stay group

	General sample (n = 508)	Very early discharge group (n = 43)	Standard length of stay group (n = 291)	Statistic significancy
Re-admission				p = 0.575*
Yes, n (%)	5 (1)	0 (0.0)	4 (1.4)	
No, n (%)	503 (99)	43 (100)	287 (98.6)	
Observation in an emergency context				p = 0.452*
Yes, n (%)	58 (11.4)	5 (11.6)	29 (10)	
No, n (%)	450 (88.6)	38 (88.4)	262 (90)	
Feeding after discharge				p = 0.415†
Breast, n (%)	343 (67.5)	33 (76.7)	194 (66.7)	
Formula, n (%)	38 (7.5)	2 (4.7)	18 (6.2)	
Mixed, n (%)	127 (25)	8 (18.6)	79 (27.1)	
Recover birth weight	(n = 490)	(n = 42)	(n = 281)	p = 0.916†
Yes, n (%)	380 (77.6)	32 (76.2)	212 (75.4)	
No, n (%)	110 (22.4)	10 (23.8)	69 (24.6)	

*Fisher exact test.
†Chi-square test.

with an odds ratio of 2.21 (95%, IC 1.29 to 3.78); birth weight < 2500g (2.3% vs 8.7%, p value < 0.005) with an odds ratio of 3.89 (95%, IC 1.46 to 10.34); gestational age < 37 weeks (1.4% vs 7.6%, p value < 0.005) with an odds ratio of 5.16 (95%, IC 1.51 to 17.66) and the need for phototherapy (0.9% vs 12.4% 95%, p value < 0.001) with an odds ratio of 15.18 (95%, IC 3.61 to 63.76).

Delay in discharge was not associated with: maternal age, with a median maternal age of 31 years in both groups; primiparity (49.3% vs 54%, p value = 0.300); presence of jaundice (56.7% vs 60.5%, p value = 0.389) and exclusive breastfeeding (85.3% vs 85.9%, p value = 0.131).

Early discharge was not associated with a higher readmission rate (0.5% vs 1.4%, p value = 0.399). Analyzing the subgroup of newborns with very early discharge (30 to 39 hours), there was also no association with a higher readmission rate (0% vs 1.4%, p value = 0.575). Excluding the variable cesarean

Table 5. Comparison of readmission rate, observation in an emergency context, feeding after discharge and recovery of birth weight between early discharge group and standard length of stay group excluding caesarean section delivery

Excluding caesarean section	General sample (n = 355)	Early discharge group (n = 200)	Standard length of stay group (n = 155)	Statistic significancy
Re-admission				p = 0.889*
Yes, n (%)	4 (1.1)	1 (0.5)	3 (1.9)	
No, n (%)	351 (98.9)	199 (99.5)	152 (98.1)	
Observation in an emergency context				p = 0.631†
Yes, n (%)	47 (13.2)	28 (14)	19 (12.3)	
No, n (%)	308 (86.8)	172 (86)	136 (87.7)	
Feeding after discharge				p = 0.276†
Breast, n (%)	243 (68.5)	136 (68)	107 (69)	
Formula, n (%)	27 (7.6)	19 (9.5)	8 (5.2)	
Mixed, n (%)	85 (23.9)	45 (22.5)	40 (25.8)	
Recover birth weight	(n = 343)	(n = 193)	(n = 150)	p = 0.095†
Yes, n (%)	264 (74.4)	155 (80.3)	109 (72.7)	
No, n (%)	79 (22.3)	38 (19.7)	41 (27.3)	

*Fisher exact test.
†Chi square test.

delivery (Table 5), as a possible confounding factor, there was also no association with a higher readmission rate (0.5% vs 1.9%, p value = 0.889).

Early discharge was not associated with a higher rate of observation in an emergency context (13.4% vs 10%, p value = 0.233) within 15-days after discharge. Analyzing the subgroup with very early discharge and excluding cesarean delivery (Table 5) there was also was no association with a higher rate of emergency observation (respectively 11.6% vs 10%, p value = 0.452 and 14% vs 12.3%, p value = 0.631).

Early discharge was not associated with a lower rate of exclusive breastfeeding (68.7% vs 66.7%, p value = 0.240) in the 15-days after hospital discharge. Analyzing the subgroup with very early discharge and excluding cesarean delivery (Table 5) there was also was no association with lower rate of exclusive breastfeeding (respectively 76.7% vs 66.7%, p value = 0.415 and 68% vs 69%, p value = 0.276). Early discharge was not associated with a higher abandonment of exclusively breastfeeding compared with discharge after 48 hours (respectively 22.7% vs 28.4%, p value = 0.180).

Early discharge was not associated with lower birth weight recovery (80.4% vs 75.4%, p value = 0.195). Analyzing the subgroup with very early discharge and excluding cesarean delivery there was also no association with lower birth weight recovery (respectively 76.2% vs 75.4%, p value = 0.916 and 80.3% vs 72.7%, p value = 0.095).

Discussion

Although early discharge is associated with benefits, the existing evidence does not allow to recommend or contraindicate this practice. Aspects such as breastfeeding adaptation, clinical conditions that only manifest themselves from the second day of life (jaundice) and mother education on the adequate newborn care represent sources of major concerns with early discharge[3-5,12]. To the best of our knowledge, this is the first Portuguese study on the impact of early discharge on newborns.

In recent years, there has been a downward trend in the average length of stay in the study, the mean length of stay for all deliveries was 2.3 days (54 hours), which is lower than the average of 2.9 days of Organization for Economic Cooperation and Development (OECD) countries and similar to the data report by Sweden and Denmark (2.3 days)[2]. In the early discharge group, the mean length of stay was 1.8 days (30 to 48 hours) and in the standard length of stay group it was 2.6 (49 to 100 hours).

Our findings are similar to the study by *Oddie* et al.[13] and show that infants were less likely to be discharged early if they were born to cesarean delivery or assisted vaginal delivery, if birth weight was lower than 2500g, gestational age inferior to 37 weeks or if they needed phototherapy. In contrast with *Oddie* et al.,[13] younger mothers, primiparous and exclusive breastfeeding weren't associated with a delay in discharge in our sample.

The global readmission rate in this study was 1% similar to the results of *Young* et al. (1.12%)[11] and *Escobar* et al. (1.0% to 3.7%)[14]. It was also similar to the readmission rate of newborns, within the first 15-days after postpartum discharge, from our hospital, in the same period (1.4%). These results contrast with results from *Farhat* et al. where the mean length of stay was 1.6 days and readmission rates were 7.9%[15]. The early discharge group was found to have a readmission rate of 0.5% and the standard length of stay group had a 1.4% readmission rate. Thus, in this study, early discharge was not associated with a higher readmission rate in the 15-days after postpartum discharge. Analyzing the subgroup of newborns with very early discharge (between 30 and 39 hours), these were also not associated with a higher readmission rate. When cesarean deliveries are excluded, as a possible confounding factor, the results remain the same. These results are similar to the report by *Benahmed* et al.[3] in their systematic literature review and contrast with the results presented by *Jones* et al.[7] in their meta-analysis, where infant readmission to hospital within 28-days after birth revealed that infants were significantly more likely to be readmitted to hospital if they were discharged less than 48 hours after birth. The *Farhat* et al.[15] study showed that early discharge was associated with an increased likelihood of readmission during the first two weeks of life as compared with later discharge. The present study identified as the cause of readmission jaundice requiring phototherapy in the early discharge group and infectious cause, weight loss and feeding difficulties in the context of laryngotracheomalacia in the standard length of stay group. The findings described above are comparable to the main causes of readmissions described by *Young* et al.[11] (feeding problems, jaundice, respiratory distress and infection). Despite what has been described, the reduced number of readmissions does not allow solid conclusions to be drawn on this specific issue.

Concerning newborns observed in an emergency context within 15-days after discharge, neither early discharge nor very early discharge were associated with a statistically significant increase in the rate of observations when compared to the standard length of stay group. These results are in line with those described by *Jones* et al.,[7] where early postnatal discharge, compared with later discharge, probably makes little to no difference in the number of infants having at least one unscheduled medical consultation or contact with health professionals within the first four weeks after birth.

A positive aspect that this study highlights from our practice is the high percentage of newborns discharged from the hospital under exclusive breastfeeding (85%), superior to the described by *McDonald* et al. (61.6%)[16], similar to the described by *Castillejos* et al. (80.2%)[17]. This practice is a strong quality indicator following the Baby Friendly Health Initiative benchmark (75%)[18]. This study showed no differences between the early discharge group and the standard length of stay group (68.7% vs 66.7%) in the exclusive breastfeeding rate within 15-days after postpartum discharge. Even when analyzing the group with very early discharges (76.7%), the findings are similar. These results are in agreement with those described by *Jones* et al.[7] and *Benahmed* et al.,[3] both showing that early discharge mothers were equally likely to breastfeed their neonates as those with standard length of stay. Early discharge also did not negatively impact the birth weight recovery (80.4% vs 75.4%). These results are in agreement with that described by *Benahmed* et al.,[3] where no significant difference was found between early discharged newborns and infants with a standard length of stay regarding weight gain in the first 10 to 20 days after postpartum discharge.

Approximately 22% of newborns abandoned exclusive breastfeeding within 15-days after discharge with no statistically significant difference between early discharge and the standard length of stay groups (22.7% in the early discharge group and 28.4% in the standard length of stay group). This is an important finding as the abandonment of exclusive breastfeeding is one of the major concerns related to early discharge. According to *Vila-Candel* et al.,[19] approximately half of the mothers who offer breastfeeding initially do not fulfill their expectations for one month. *Vila-Candel* et al.[19] and *Oliver-Roig* et al.[20] report that the most critical time point for abandonment is the first 12 days of the infant's life.

In this study, early discharge was not associated with a higher readmission rate, a lower rate of adherence to exclusive breastfeeding or a higher rate of observation in an emergency context in the 15-day period after discharge, when compared to standard length of stay. On the other hand, a lower probability of early discharge was associated with cesarean delivery; assisted vaginal delivery; birth weight < 2500g; gestational age < 37 weeks and the need for phototherapy. Although there was no statistically significant difference when analyzing the subgroup of newborns delivered by cesarean section, the remaining factors should be considered when the newborn is discharged, as they are well-established risk factors for readmission.

Early discharge is the gold standard in several European countries, supported by a well-established surveillance network. The frequent evaluation of the newborn in the first weeks of life requires the recruitment of important human and financial resources in the structure of the national health system. The reduction of costs related to shorter hospital length of stay should be taken into account when allocating these resources to the care of the mother and newborn. The evaluation of the newborn, close to its family environment, should always be privileged.

This is a single institution study on a level II hospital, and, therefore, the results may not be generalizable to the Portuguese pediatric population. Thus, larger, multi-center studies on this topic are important for a better understanding of the impact of early discharges, in order to allow the creation of robust recommendations on this subject.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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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

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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Ethical disclosures

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

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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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

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.

Ethical disclosures

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

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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Vitamin B12 deficiency: an unusual presentation. Case report

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Abstract

Vitamin B12 or cobalamin is a water-soluble vitamin absorbed in the terminal ileum after binding to intrinsic factor and has important physiologic roles in haematopoiesis, intermediary metabolism, growth, and early brain development. Vitamin B12 deficiency usually causes anaemia, macrocytosis, leukopenia, hyper-segmented neutrophils, and thrombocytopenia. Although most of the vitamin B12-deficient cases have only mild haematological findings, in approximately 10% of patients, life-threatening conditions, such as symptomatic pancytopenia, severe anaemia (haemoglobin level < 6 g/dL), and haemolytic anaemia, have been reported. Since the clinical findings of B12 deficiency are nonspecific, they are often overlooked, leading to a delay in the diagnosis. In this report we describe the case of a 16-year-old boy who presented with severe haemolytic anaemia and pancytopenia secondary to vitamin B12 deficiency, which resolved completely following appropriate replacement therapy.

Keywords: Vitamin B12 deficiency. Haemolytic anaemia. Pancytopenia. Adolescent. Case report.

Défice de vitamina B12: uma apresentação invulgar. Caso clínico

Resumo

A vitamina B12 ou cobalamina, é uma vitamina hidrossolúvel, absorvida no íleon terminal, após ligação ao fator intrínseco, e desempenha um papel fisiológico importante na hematopoiese, metabolismo intermediário, crescimento e desenvolbolmento cerebral. O défice de vitamina B12, geralmente causa anemia macrocítica, leucopenia, neutrófilos hipersegmentados e trombocitopenia. Embora na maioria dos casos o défice de vitamina B12 produza apenas achados hematológicos ligeiros, em aproximadamente 10% dos casos, foram descritos condições ameaçadoras da vida, como pancitopenia sintomática, anemia grave (hemoglobina < 6 g/dL) e anemia hemolítica. Uma vez que os achados de défice de vitamina B12 são inespecíficos, são mutias vezes subvalorizados, levando a um atraso no diagnóstico. Neste artigo, descrevemos o caso de um adolescente de 16 anos, que se apresentou com anemia hemolítica grave e pancitopenia secundárias a défice de vitamina B12, achados que resolveram completamante após terapêutica de reposição apropriada.

Palavras-chave: Défice de vitamina B12. Anemia hemolítica. Pancitopenia. Adolescente. Caso clínico.

Keypoints

What is known
– Vitamin B12 deficiency is a rare a but treatable cause of pancytopenia.
– The clinical features of cobalamin deficiency are unspecific and may involve both haematological, and neurological systems.
– The clinical presentation of vitamin B12 deficiency can mimic leukaemia, hemophagocytic lymphohistiocytosis, and thrombotic microangiopathy.

What is added
– It is important to include vitamin B12 deficiency in the differential diagnosis of severe anaemia, even in the absence of strict vegetarianism.
– Vitamin B12 deficiency can be the cause of severe anaemia despite the absence of typical haematological findings, as in this patient, where at presentation typical findings of megaloblastic anaemia were not clear in the blood count or peripheral blood smear.
– A correct diagnosis, and timely treatment can prevent long-term damage, even in cases where severe haematological findings are already present.

Introduction

Vitamin B12, or cobalamin, is a water-soluble vitamin which is synthesized by bacteria and archaea. It is absorbed in the terminal ileum after binding to intrinsic factor, which is produced by the parietal cells in the stomach. Vitamin B12 deficiency usually causes anaemia, macrocytosis, leukopenia, hyper-segmented neutrophils, and thrombocytopenia[1].

Although most of the vitamin B12-deficiency cases have only mild haematological findings, in approximately 10% of patients, life-threatening conditions such as symptomatic pancytopenia, severe anaemia (haemoglobin level < 6 g/dL), and haemolytic anaemia have been reported[2].

In this report we describe the case of a 16-year-old boy who presented with severe haemolytic anaemia and pancytopenia secondary to vitamin B12 deficiency, which resolved completely following appropriate replacement therapy.

Case report

A 16-year-old, previously healthy, black male was brought to the emergency department (ED) with fever, and incoherent speech. In the week preceding the admission he had been suffering with abdominal pain, and vomiting. For this reason, he had already accessed primary care and was given probiotics and oral rehydration solution. Additionally, his brother mentioned an unquantified unspecified weight loss during the previous month. He had no history of dietary restrictions, no smoking, alcohol, or drug intake habits. There was no mention of nitrogen protoxide use, but it was not specifically asked.

Physical examination on the ED was remarkable for a Glasgow Coma Scale of 12, with no other neurological signs, muco-cutaneous paleness, icterus of the sclera, and enlarged spleen and liver with no other significant findings.

A preliminary laboratory investigation revealed pancytopenia (haemoglobin 3g/dL [N13-17], Mean Corpuscular Volume [MCV] 93 fL, leucocytes 2,96 x 10 ^ 9/uL [N 4,5-13] with neutrophils 980 x 10 ^ 9/uL [N 1500-8000] and lymphocytes 1550 x 10 ^ 9/uL [N 1000-4800], platelets 75 x 10 ^ 9/uL [N 150-400], reticulocytes 3,1% [N < 2]); high serum levels of indirect bilirubin (2.05 mg/dL N [0-0.8]), lactate dehydrogenase > 5000 U/L (N 135-225), aspartate aminotransferase 100 U/L (N 8-40). Coagulation values were normal (prothrombin time 13.8s [N 11.4-13.8], activated thromboplastin time 22,8s [N 21.4-31.2s] and INR 1.22). Fibrinogen was also within a normal range of 181 mg/dL (N 108-350). Kidney function was preserved with a urea 24 mg/dL and creatinine 0.59 mg/dL.

The peripheral blood smear showed anisocytosis, poikilocytosis with schistocytes, target cells, pencil cells, and erythroblasts (25/100 leucocytes). Uric acid, C reactive protein were normal. Direct Coombs test was negative. The chest X-ray was normal.

Treatment was started immediately with red blood cell transfusion (20ml/kg), and platelet pool transfusion. At this point 4g IV plasma, and IV fibrinogen reposition (1g) were also started, prior to the clotting laboratory results being known, due to concerns as to a possible hidden haemorrhage.

After the red blood cell transfusion, the adolescent showed signs of neurological improvement, with a GCS of 14, and was admitted for further investigation.

A more detailed etiological study showed a low vitamin B12 with 146pg/mL (N 211-911pg/mL). Homocysteine and methylmalonic acid were not obtained before starting treatment. Bone marrow aspiration ruled out leukaemia and the smear was compatible with megaloblastic anaemia. Normal activity levels for ADAMTS 13 excluded thrombocytopenic thrombotic purpura. Hemophagocytic

lymphohistiocytosis was dismissed since ferritin, fibrinogen, CRP, and triglycerides were within normal range, and bone marrow aspiration showed no signs of hemophagocytosis or macrophage infiltrates. Recent infection with Epstein-Barr virus, cytomegalovirus, or parvovirus B19 were ruled out by serology.

The cause of the vitamin B12 deficiency has yet to be determined, even after extensive investigation. The clinical history was revised with the patient and his family, establishing that he did not follow a strict vegan diet. There was no evidence of pernicious anaemia since the search for helicobacter pylori was negative and both the intrinsic factor and parietal cell antibodies were negative. The anti-transglutaminase IgA antibody was negative, which allowed us to exclude celiac sprue as well. Inflammatory bowel disease was ruled out after faecal calprotectin level, and upper GI tract endoscopy and colonoscopy were all normal, with biopsies exhibiting no abnormal findings. Intestinal parasitosis was also excluded as no helminths or protozoa were found in faecal testing.

Oral folic acid supplementation and daily Vitamin B12 IM administration was started and after 14 days the patient showed clinical improvement with complete neurologic recovery and significant weight gain (5.5 kg, about 9% of total body weight).

Upon discharge, he kept regular follow-up in the haematology clinic. There has been no recurrence of symptoms, with sustained values for haemoglobin with monthly cobalamin IM administrations.

Discussion

Clinical and haematological improvement upon supplementation with both vitamin B12 and folate after immediate transfusion with 20ml/kg red blood cells, as well as extensive etiological investigation with no other significant findings other than low levels of cobalamin and a bone marrow smear with aspects compatible with megaloblastic anaemia support vitamin B12 deficiency as the cause for this presentation, even though the cause of this deficiency has yet to become clear.

Although the patient was not strictly vegetarian, the family struggled economically, leading to an imbalanced diet which might have caused this vitamin deficit. Supporting this hypothesis is the nutritional study with low pre-albumin level (13.6 g/dL) and low serum total protein levels (5.9 g/dL), despite an albumin within normal range (4 g/dL).

The cause of the fever at presentation was not determined, but normal CRP levels and negative blood, urine, and stool cultures and a normal chest radiography excluded bacterial infection, with a viral etiology becoming more likely and possibly triggering the clinical presentation of severe chronic anaemia.

Vitamin B12 has important physiological roles in haematopoiesis, intermediary metabolism, growth, and early brain development[3,4]. The human species does not synthesize B12, so exogenous intake is crucial[5], and an inadequate dietary intake or impaired absorption are the most common causes of B12 deficiency[6].

Clinical features of B12 deficiency may include, besides the macrocytic anaemia, neurological, and gastrointestinal symptoms such as lethargy, hypotonia, psychomotor delay or regression; tremor; seizures; encephalopathy; irritability; weakness; diarrhoea; stomatitis; glossitis, and failure to thrive[3-8].

Since these clinical findings of B12 deficiency are nonspecific, they are often overlooked, leading to a delay in the diagnosis. Although supplementation with vitamin B12 quickly reverses the haematological abnormalities, the neurological manifestations may not completely resolve if not treated promptly[3,7].

This case is an example of an uncommon presentation of vitamin B12 deficiency and shows the importance of searching for this vitamin deficiency in such clinical settings and treating it despite not having completely clarified the cause, as a timely recognition and appropriate treatment are fundamental for the complete remission of symptoms and prevention of long-time damage.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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Enlarged parietal foramina: a case report

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Abstract

Enlarged parietal foramina is a rare entity that results from late or incomplete ossification, ending as large foramina in the parietal bone. Usually, affected children are asymptomatic but may present with severe headache, vomiting or predisposition for epilepsy. This case aims to raise awareness of a rare clinical entity that can be manifested by a persistently opened posterior fontanelle. The prognosis is mostly benign.

Keywords: Parietal foramina. Posterior fontanelle. Autosomal dominant. Benign.

Foramina parietalia permagna: caso clínico

Resumo

Foramina parietais alargados representam uma entidade rara que resulta de ossificação tardia ou incompleta, culminando num defeito ósseo de grandes dimensões no osso parietal. Geralmente, as crianças afetadas são assintomáticas, podendo no entanto apresentar-se com cefaleia, vómitos ou predisposição para epilepsia. Este caso tem como objetivo alertar para uma entidade clínica rara que pode manifestar-se por uma fontanela posterior persistentemente aberta. O prognóstico é geralmente benigno.

Palavras-chave: Foramina parietais. Fontanela posterior. Autossómica dominante. Benigno.

The authors report the case of a 2-day-old girl discharged from a newborn nursery to ambulatory care for surveillance of an enlarged posterior fontanel. She was born full-term after an uneventful pregnancy and normal vaginal delivery. Physical examination revealed a non-dysmorphic female with normal neurologic examination, a bilateral hip clunk and an open posterior fontanel measuring 1.5 x 1cm. Posterior fontanel was studied at first in neonatal period because of its large diameter and after that due to its persistence. Calcium/ phosphorus metabolism and thyroid function were normal. Transfontanellar ultrasound showed a periventricular cyst and hip ultrasound evidenced bilateral developmental dysplasia that required surgery. At 8 months old, the patient was referred to a Neurosurgery center and a cranial CT-scan demonstrated a bilobed bone defect suggesting enlarged parietal foramina, as ilustrated in Figures 1 and 2. There was no relevant family history except for the fact that the patient's father had scaphocephaly, without comorbidities. Watchful
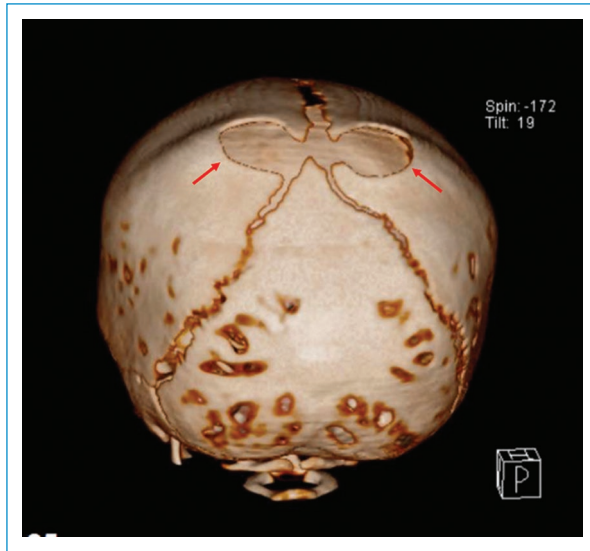
Figure 1. Cranial CT-scan with 3D reconstruction demonstrating a bilobed bone (red arrows).
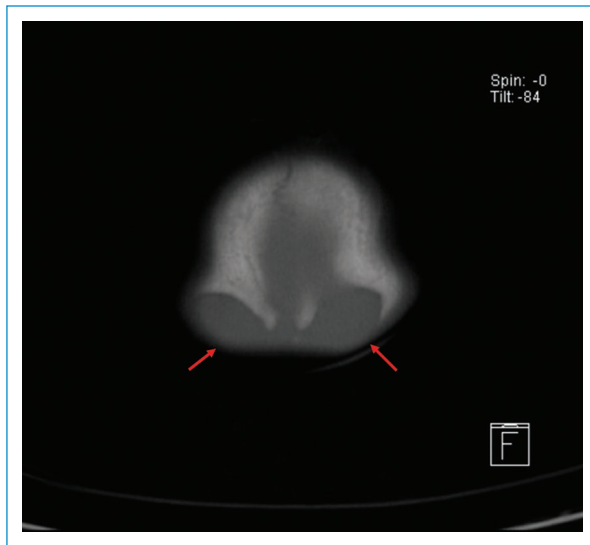
Figure 2. Bone window image of a cranial CT-scan demonstrating a bilobed bone (red arrows).

with a prevalence of 1:15.000-1:50.000[1]. It results from late or incomplete ossification[1,2] ending as large foramina in the upper posterior angle of parietal bone close to the intersection of sagittal and lambdoid sutures[1]. Typically oval or round, enlarged parietal foramina resemble a "pair of spectacles" on postero-anterior skull radiographs and 3D CT scanning using bone windows clearly reveals the defect[3]. Mutations of MSX2 (in 5q34-35) or ALX4 (in 11p11) genes are associated[1,3]. Usually, affected children are asymptomatic but may present with severe headache, vomiting or predisposition for epilepsy[1,3]. It also can be seen associated with anomalies such as myelomeningocele, cleft palate, vascular malformations of the posterior fossa[1] and abnormal venous drainage[2]. Differential diagnosis includes Potocki-Shaffer syndrome, ALX4-related frontonasal dysplasia, MSX2-related craniosynostosis, distal 5q deletions, all including intellectual disability, growth and developmental delay[1]. Apart from genetic disorders, enlarged parietal foramina appears in fetal methotrexate syndrome[1]. This case aims to raise awareness of a rare clinical entity that can be manifested by a persistently opened posterior fontanelle. The prognosis is mostly benign with cranioplasty reserved for very active children, due to risk of trauma, or in cases with associated co-morbidities, such as epilepsy[1].

Awards and previous presentations

The case report was not presented before the submission of the manuscript and prizes were not awarded.

waiting was recommended with periodic follow-up and parental advice concerning trauma prevention. Genetic testing was not performed. She was followed by both Pediatrics and Neurosurgery until the age of 3, maintaining daily annual follow-up by Neurosurgery. She is now 6 years old and has always remained asymptomatic with normal neurodevelopment and growth including head circumference. Enlarged parietal foramina is a rare, autosomal dominant defect with incomplete penetrance,

or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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Acute Q fever and pulmonary tuberculosis in pediatric age: a case report

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Abstract

In pediatric age groups, fever of unknown origin composes a diagnostic challenge due to its multiple possible etiologies. A high percentage of those cases is caused by infections. In this article, we describe the clinical case of an adolescent with atypical pneumonia caused by simultaneous infection of *Coxiella burnetti* and *Mycobacterium tuberculosis*. In children, tuberculosis is a known cause of prolonged fever and high mortality. Diagnosis of Q fever is less prevalent, but its importance has been highly increasing. The clinical picture outlined here improved after pursuing the treatment for acute Q fever. Nevertheless, it is essential to emphasize the importance of identification and treatment for both infections. This association is rare since this is the third case reported in the literature and the first one in pediatric age.

Keywords: Fever of unknown origin. Pediatrics. Q Fever. Tuberculosis. Zoonoses. Case reports.

Febre Q aguda e tuberculose pulmonar em idade pediátrica: um caso clínico

Resumo

A febre de origem desconhecida representa um desafio diagnóstico, com múltiplas possíveis etiologias em idade pediátrica. Uma grande percentagem dos casos é de causa infeciosa. Neste artigo descrevemos o caso clínico de um adolescente com pneumonia atípica causada por infeção simultânea por *Coxiella burnetii* e *Mycobacterium tuberculosis*. Em idade pediátrica, a tuberculose é uma reconhecida causa de febre prolongada e elevada mortalidade. O diagnóstico de febre Q é menos prevalente, mas tem assumido importância crescente. O quadro clínico exposto evoluiu favoravelmente após tratamento dirigido para a febre Q aguda, mas salienta-se a importância da identificação e tratamento de ambas as infeções. Esta associação é rara, sendo este o terceiro caso reportado na literatura e o primeiro em idade pediátrica.

Palavras-chave: Febre de origem desconhecida. Pediatria. Febre Q. Tuberculose. Zoonoses. Caso clínico.

Keypoints

What is known
– Most cases of fever of unknown origin are caused by infections. In children, tuberculosis is a known cause of prolonged fever and high mortality. Diagnosis of Q fever is less prevalent.

What is added
– Even in the absence of epidemiological context, it is important to consider the diagnosis of Q fever and tuberculosis. Notified cases of Q fever underestimate the prevalence of this diagnosis. Reported simultaneous infection by *C. burnetti* and *M. tuberculosis* is rare.

Introduction

Fever is one of the most common signs of illness in children[1]. When it has a prolonged course and its cause is not identified after anamnesis, detailed physical exam, and initial investigation, we are in the presence of fever of unknown origin (FUO)[1]. This entity can be caused by multiple disorders, infectious diseases being the most frequent etiology. Atypical pneumonia can be one of the causes and its clinical, analytical and imagiological manifestations often do not predict the diagnosis[1,2].

Previously considered a rare disorder, limited to certain population groups, Q fever has assumed increasing importance as a cause of FUO[3]. Since its introduction as a notifiable disease in Portugal, only 217 cases have been reported in 15 years[4]. However, serologically, there was a much higher number of infections[5].

Pulmonary tuberculosis can also cause prolonged fever[1]. Due to the immaturity of their immune system, 40% of infected children develop the disease, which explains the higher prevalence of this diagnosis[6,7].

Case report

We report a case of a 12-year-old male adolescent, previously healthy and with history of tuberculosis vaccine, resident in a suburban area in Bordeaux, France. He denied any contact with animals, ingestion of unpasteurized foods or epidemiological context of disease.

Observed at his local hospital with two days of fever, dry cough and headache, he was diagnosed with pneumonia and discharged home with amoxicillin. Due to sustained fever after 72 hours on this antibiotic, clavulanic acid was added to the treatment.

In Portugal, due to persistent fever on day-four of amoxicillin/clavulanic acid, he was taken to the emergency department. His physical examination was significant for crackles at the base of the right lung on pulmonary auscultation, but showed hemodynamic stability, good general state, no signs of respiratory distress and adequate peripheral oxygen saturation in ambient air.

An analytical study revealed 21210 leukocytes/uL with 17070 neutrophils/uL and C-reactive protein of 105.8 mg/L, with no other abnormalities. Chest radiography showed hypotransparency in the right lung base. An ultrasound confirmed this consolidation and discarded any associated complications.

On the suspicion of atypical pneumonia, he was admitted for intravenous antibiotic therapy with ceftriaxone.

As the fever persisted on day three of admission, analytical and imagiological evaluation was repeated, showing maintained leukocytosis and C-reactive protein elevation, sedimentation rate of 56 mm/h and bilateral interstitial infiltrates on chest radiograph. Clindamycin and azithromycin were added to the therapeutics.

After a week of hospitalization and sustained fever, a thoracic computed tomography was requested, revealing extensive areas of parenchymal consolidation, with bibasal predominance but also affecting the upper segments, multiple cavitated areas and diffuse tree-in-bud pattern.

It was decided to extend the etiological study, suspend ongoing therapeutic and start doxycycline. After eight days of treatment, the patient became apyretic.

Blood cultures on day nine and day seventeen of disease, virological examination of nasopharyngeal aspirate and *Legionella pneumophila* urinary antigen were negative. There was no serological evidence of acute CMV, EBV, parvovirus B19 or *Brucella* infection. *Coxiella burnetti* serologies revealed IgG phase II > 800, fulfilling diagnostic criteria for acute Q fever. From the study directed to *Mycobacterium tuberculosis*, *Mantoux* test was negative, IGRA was positive and molecular biology and culture in bronchoalveolar lavage were positive.

Considering the diagnosis of acute Q fever, an echocardiogram was performed, showing no abnormalities, and antibiotic therapy was maintained for 14 days. In the face of the concomitant diagnosis of pulmonary tuberculosis, the patient was referred to the regional referral center and is currently undergoing targeted therapy.

Discussion

In this article, we describe a case of concomitant acute Q fever and pulmonary tuberculosis, two disorders

of challenging diagnosis in the absence of evident epidemiological context.

Q fever is a zoonosis with a worldwide distribution caused by the bacterium *C. burnetii*, whose main route of human transmission is inhalation of aerosols contaminated with excreta from farm animals[8]. Although in the present case no direct contact with possible reservoirs was identified, the outbreak of acute Q fever in the Netherlands between 2007-2010 indicated that this is not required, since the bacterium has a highly resistant sporiform phase in its life cycle, which can cause infection within 2 km of the infectious source[8,9].

The transmission of *M. tuberculosis* occurs by inhalation of aerosolized particles and the diagnostic suspicion arises, in most cases, from contact with a patient with active tuberculosis[1,6]. Although, in this case, the epidemiological history was negative, the clinical course and imagiological findings made this a mandatory differential diagnosis.

It is difficult to distinguish which of the infections was responsible for the patient's symptoms. The clinical presentation of acute Q fever is highly variable, the infection being asymptomatic in 50% of cases, with an even higher percentage in pediatric age[8]. Among symptomatic patients, the most frequent presentation is a self-limited febrile illness, associated with findings of pneumonia or hepatitis[8]. The diagnosis is made, in the first two weeks of the disease, by detection of bacterial DNA in the blood by PCR or, later, by detection of high or quadrupled IgG phase II titers in relation to the previous sample by indirect immunofluorescence[8]. The clinical response to doxycycline, the first-line therapy in children over eight years of age, suggests that the fever was the result of *C. burnetii* infection[8]. Thus, and considering that infections are one of the most immunologically disturbing events in pediatric age, we can interpret pulmonary tuberculosis as a consequence of the reactivation of the latent bacillus in a previously balanced immune system[10]. Regardless of the infection that determined the patient's clinical picture, we highlight the importance of identifying and treating both diseases. Despite the good prognosis of acute Q fever, with a reported mortality of less than 2% and development of persistent disease in only 5% of cases, chronic infection, in most cases in the form of endocarditis, implies a challenging treatment with high mortality[8]. Tuberculosis is the tenth leading cause of death worldwide, with 16% of all deaths occurring in children[11].

Simultaneous infection by these two microorganisms is rare, this being the third case reported in the literature and the first case described in pediatric age[12,13]. In adulthood, this co-infection also caused prolonged fever, associated with hepatitis in the case of Sumida et al.[12] and atypical pneumonia in the report by Simões et al.[13]

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Lane-Hamilton syndrome: a case report

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Abstract

Idiopathic pulmonary hemosiderosis is an uncommon disease of childhood, manifesting with the triad of recurrent hemoptysis, diffuse parenchymal infiltrates on chest radiographs and iron deficiency anemia. Celiac disease is an enteropathy characterized by life-long intolerance to ingested gluten in genetically susceptible people. In 1971 Lane and Hamilton first described the association of idiopathic pulmonary hemosiderosis with celiac disease and since then a few isolated cases have been reported in literature. We report a child with pulmonary hemosiderosis presenting with hemoptysis, severe anemia, and diffuse alveolar infiltrates in whom we made a diagnosis of celiac disease. In our case, severe anemia and alveolar infiltrates markedly improved with gluten-free diet.

Keywords: Idiopathic pulmonary hemosiderosis. Celiac disease. Lane-Hamilton syndrome. Case report.

Síndrome de Lane-Hamilton: reporte de un caso

Resumo

A hemossiderose pulmonar idiopática é uma doença rara em idade pediátrica, caraterizada por hemoptises recorrentes, infiltrados difusos no parênquima pulmonar na radiografia torácica e anemia ferropénica. A doença celíaca é uma enteropatia caraterizada por intolerância ao glúten em pessoas geneticamente suscetíveis. Em 1971, Lane e Hamilton descreveram o primeiro caso que associava a hemossiderose pulmonar com a doença celíaca e, desde então, um pequeno número de casos tem sido descrito na literatura. Reportamos um caso clínico de uma criança com hemossiderose pulmonar caraterizada por hemoptises, anemia grave e infiltrados difusos no parênquima pulmonar a quem foi diagnosticada doença celíaca. A anemia severa e os infiltrados alveolares resolveram com a introdução de uma dieta isenta de glúten.

Palavras-chave: Hemossiderose pulmonar idiopática. Doença celíaca. Síndrome Lane-Hamilton. Relato de caso.

Keypoints

What is known

– Idiopathic pulmonary hemosiderosis is an uncommon disease of childhood manifesting with the triad of recurrent hemoptysis, diffuse parenchymal infiltrates on chest radiographs and iron deficiency anemia.
– Idiopathic pulmonary hemosiderosis has been associated with celiac disease in rare cases.

What is added

– Patients with idiopathic pulmonary hemosiderosis should be screened for celiac disease, even if there are no symptoms of gastrointestinal disease.
– A high index of suspicion for pulmonary hemosiderosis should be kept in patients of celiac disease with disproportionately severe anemia.
– Early recognition of Lane-Hamilton syndrome and initiation of treatment with a gluten-free diet may result in disease remission and may prevent progressive pulmonary disease.

Introduction

Although hemoptysis is a rare condition in infants and children, it is potentially life-threatening and may cause significant morbidity. Unless the volume of blood is considerable, hemoptysis may be difficult to detect because younger children, especially infants, swallow their sputum. However, once identified, the source and underlying pathology must be investigated in a systematically manner[1]. The differential diagnosis for hemoptysis is extensive, ranging from relatively common to quite rare conditions. Possible etiologies include infection, bronchiectasis, non-pulmonary bleeding, trauma, coagulopathy, cardiac disease, pulmonary tumor, vascular anomaly, autoimmune disease, and pulmonary-renal syndromes[2,3].

Idiopathic pulmonary hemosiderosis (IPH) is an uncommon disease of childhood, with an incidence varying from 0.24 to 1.23 patients per million children[4,5], manifesting with the triad of recurrent hemoptysis, diffuse parenchymal infiltrates on chest radiographs and iron deficiency anemia[4,5]. Recurrent alveolar bleeding may eventually produce pulmonary hemosiderosis and fibrosis. Diagnosis of IPH requires evidence of diffuse alveolar hemorrhage (DAH) and exclusion of other causes (Table 1)[6].

Celiac disease (CD) is a common immune-mediated enteropathy driven by dietary gluten and related proteins in genetically predisposed individuals. In over half of the patients, CD presents with extra-intestinal manifestations, most commonly short-stature, anemia, delayed puberty, liver abnormalities, dental enamel defects, aphthous stomatitis, myopathy, arthralgias, and synovitis. In the rarest forms CD includes headaches, ataxia, neuropathy, and seizures with bilateral occipital calcifications, osteopenia, and osteoporosis, hyposplenism, infertility, dermatitis herpetiformis, and alopecia. Hemorrhagic events, such as gastrointestinal hemorrhage, hematuria, epistaxis, and hemoptysis are the most uncommon presentations of CD[7-13].

Case report

A 12-year-old healthy girl presented a 6 month not explained/investigated history of intermittent hemoptysis, cough, and upper respiratory tract symptoms. One month before, she was suffering from recurrent and diffuse abdominal pain, fatigue, and dizziness. She was admitted to our paediatric unit due to persistent periumbilical and right iliac fossa pain with 24 hours evolution. She had normal menses and denied epistaxis, black or tarry stools, and easy bleeding. There were no changes in stool patterns, fevers, night sweats, and weight loss. The personal and family medical history was unremarkable. There was no history of close contact with any tubercular patient.

She was in reasonable general health, had moist and discolored mucous membranes, had no jaundice or cyanosis, and breathed normally. Her vital signs were within normal limits, and her SpO2 was 98% on room air. Her weight was 45 kg (50-75 percentile), height 158 cm (50-75 percentile), and body mass index 18kg/m^2 (25-50 percentile). Cardiopulmonary and neurological examination revealed no abnormalities. Abdominal examination revealed localized tenderness and muscular rigidity to the right iliac fossa. She had no skin lesions, joint lesions, peripheral edema, or digital clubbing.

Lab investigations showed: severe microcytic, hypochromic anemia (Hb = 6 g/dL); total leukocyte count 10.93 × 10^9/L with 73.3% polymorphs and 18.9% lymphocytes; platelet count 205 × 10^9/L. Coagulation profile, renal and liver function tests were normal.

Table 1. Causes of diffuse alveolar hemorrhage

Disorders with capillaritis	Disorders without capillaritis	
	Cardiovascular causes	Non-cardiovascular causes
– Granulomatosis with polyangiitis (Wegener) – Microscopic polyangitis – Systemic lupus erythematosus – Goodpasteurs disease – Henoch-Schönlein purpura – IgA nephopathy – Behçet syndrome – Cryoglobulinemia – Drug-induced capillaritis – Idiopathic lung-kidney syndrome – Idiopathic pulmonary capillaritis	– Mitral stenosis – Pulmonary veno-occlusive disease – Arteriovenous malformation – Pulmonar lymphangioleiomyomatosis – Pulmonary hypertension – Pulmonary capillary hemangiomatosis – Chronic heart disease – Pulmonary infarction	– Idiopathic pulmonary hemosiderosis – Heiner syndrome – Celiac disease – Coagulopathies – Hematopoietic cell transplantation

Sedimentation rate was 6 mm/hour, C-reactive protein 0.10 mg/dL. The mean corpuscular volume was 60.9 fL, reticulocyte count 1,25 %, serum iron 8 μg/dL, total iron-binding capacity (TIBC) 413 μg/dL, ferritin 23.5 ng/mL. The peripheral smear examination showed hypochromic microcytic anemia. Urine examination did not reveal albuminuria or hematuria.

Computed tomography (CT) revealed an ileocecal appendix, approximately 10mm wide, with same slight densification of the surrounding fat. Moreover, there were signs of a ground glass appearance of the lung bases with unspecific features. Suspicion of acute appendicitis led to the patient's transfer to the Pediatrics Surgery Observation Unit. When the patient was admitted, an abdominal ultrasound was performed that also suggested the diagnosis. In addition, chest radiograph showed bilateral diffuse alveolar infiltrates.

Red blood cells transfusion was performed before laparoscopic appendectomy, which confirmed an acute appendicitis's initial stages.

Additional studies revealed unremarkable vitamin B12, folate, haptoglobin, and uric acid levels. Antinuclear, anti-neutrophil cytoplasmic (p-ANCA and c-ANCA), and rheumatoid factor were negative. C3 and C4 levels were normal. Serologic tests for Epstein-Barr virus, cytomegalovirus, and parvovirus B19 were negative.

During her stay at the hospital, the patient remained hemodynamically stable, in sustained apyrexy. She recovered from the fatigue, and dizziness and did not show any signs of bleeding during the hospitalization.

She was given parenteral iron supplementation - Hg 7.7g/dL on the discharge date. She was discharged home after 5 days, with instructions to complete parenteral iron supplementation (200 mg elemental iron per infusion, three infusions, every 2 days).

A pulmonary CT was performed after discharge, which revealed bilateral diffuse alveolar infiltrates over middle and lower zones and ground glass opacities suggestive of hemosiderosis or hemorrhage (Figs. 1, 2 and 3). Lung function tests were within the normal range. Sputum examination for bacteria and mycobacteria was negative. IGRA test and allergology studies were negative. There were also no signs of hemosiderin, but the sample showed a small amount of blood.

Tissue transglutaminase IgA (TTGA) titer was 2400 U/mL (normal: < 10 U/mL) and anti-deamidated gliadin titer was 220 U/mL (normal: < 7 U/mL). A duodenal biopsy revealed total villous atrophy and intense lymphocyte and plasmocyte infiltration at lamina propria consistent with a diagnosis of CD (type 3C in Marsh Classification). Thus, a gluten-free diet was initiated.

Within six months, there was resolution of the pulmonary lesions in the pulmonary CT. Based on this, a final diagnosis of Lane-Hamilton syndrome was made. Due to the favorable clinical evolution of the patient, a bronchoscopy was considered unnecessary.

After two years of follow-up, the patient is doing well, without anemia, and no evidence of recurrent alveolar hemorrhage. During this period, an improvement of gastrointestinal symptoms, weight and height gain, and a reduction of antibody titer was reported (Table 2).

Discussion

The association of IPH with CD was initially identified in a young adult by Lane and Hamilton in 1971, who proceeded to call it the "Lane-Hamilton syndrome". This is an extremely rare condition, therefore there is a limited number of case reports of this syndrome in the literature[5,8-9]. Several retrospective

Figure 1. Bilateral diffuse alveolar infiltrates over middle and lower zones and ground glass opacities.
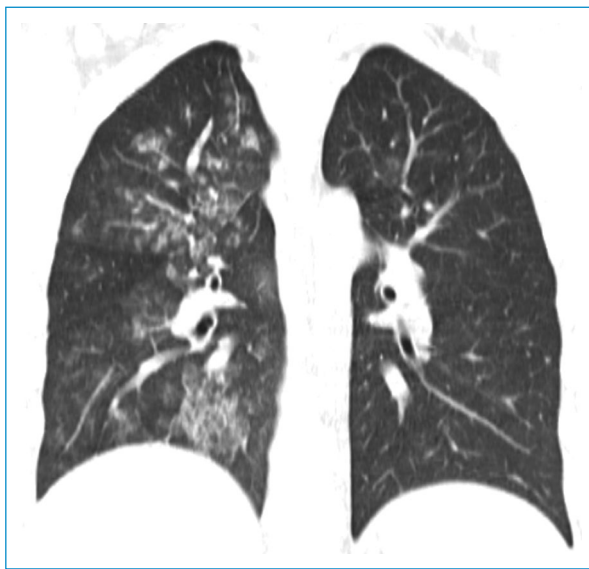
Figure 2. Bilateral diffuse alveolar infiltrates over middle and lower zones and ground glass opacities.
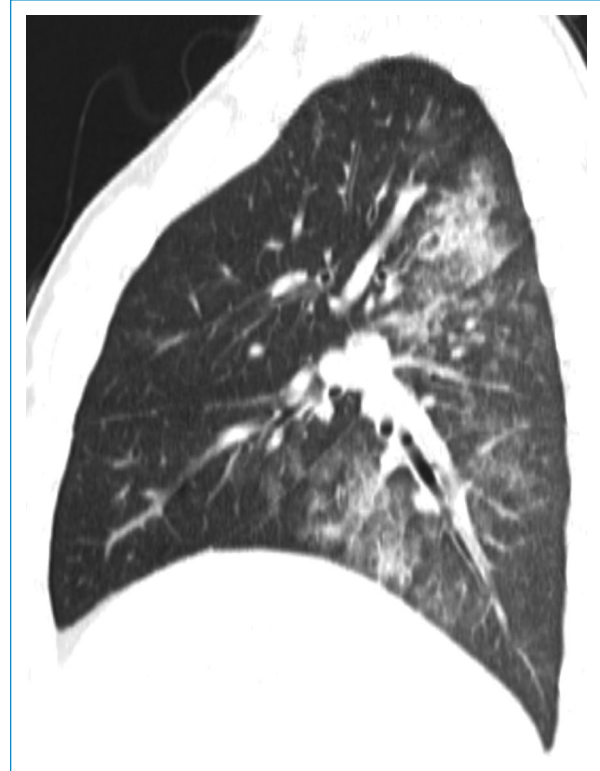
Figure 3. Bilateral diffuse alveolar infiltrates over middle and lower zones and ground glass opacities.

Table 2. Clinical evolution

	Admission	2 years of follow-up
Weight	45 kg (50-75 percentile)	61 kg (75-90 percentile)
Body mass index	18 kg/m^2 (25-50 percentile)	24 kg/m^2 (75-90 percentile)
Hemoglobin	6 g/dL	13.4 g/dL
Tissue transglutaminase IgA	2400 U/mL	44 U/mL
Anti-deamidated gliadin	220 U/mL	4.3 U/mL

observational studies have reported the prevalence of celiac antibodies in pediatric patients with IPH[8]. Remarkably, only half of these children presented gastrointestinal symptoms in addition to recurrent hemoptysis[2,10].

Lane-Hamilton syndrome has been considered an association of two different disease entities, but whether there is a unifying mechanism in the pathogenesis of both disease entities is currently unknown[8]. Hemosiderosis in celiac disease is likely to occur due to the deposition of

immune complexes involving an auto-antigen like gluten on the alveolar basement membrane or to direct reaction between the antigen of alveolar basement membrane and an antibody like the anti-reticulin one[6]. Additionally, a specific strain of adenovirus has been proposed as another pathogenic mechanism[5]. Thus, while it is commonly suggested that LHS represents the overlap of two separate disease processes, IPH and celiac disease,

others have suggested that LHS should be considered as a single disease entity[2].

In Lane-Hamilton syndrome, a gluten-free diet (GFD) is the mainstay of therapy. The clinical importance of this diagnosis is that a significant improvement can be obtained with GFD not only in intestinal but also in pulmonary symptoms. IPH can be a difficult disease to treat, and previous studies suggest that the treatment is often complicated by frequent recurrences and sometimes the development of end-stage lung disease requires lung transplantation. However, in Lane-Hamilton syndrome, the use of GFD can result in partial or complete cessation of lung hemorrhage, reduce the need for blood transfusions and steroid therapy, and leads to radiological improvement in most individuals, as seen in this case[8,10-12]. For those who do not respond to a gluten-free diet, immunosuppressive therapy may be necessary. The typical first-line immunosuppressive treatment for IPH are systemic steroids. Additional treatment options include hydroxychloroquine, cytotoxic agents, or a combination of one of these medications with systemic steroids[2]. Long-term nutritional follow-up is also important; it has been reported that poor adherence to the diet can reactivate respiratory and gastrointestinal symptoms[11,13]. Lane-Hamilton syndrome results in significant morbidity and mortality once recurrent alveolar hemorrhage may result in progressive pulmonary fibrosis if left untreated[8,14,15].

In conclusion, a high index of suspicion for celiac disease should be kept in patients with pulmonary hemosiderosis, especially with disproportionately severe anemia in spite of absence of gastrointestinal symptoms and vice-versa. Therefore, all patients diagnosed with IPH should be screened for CD by serologic assays, which are very sensitive, and any respiratory illness associated with aggravation of anemia should prompt a pulmonologist to actively look for hemosiderosis. This can be safely and non-invasively done by histopathological examination of sputum/induced sputum for hemosiderin laden macrophages and a gluten-free diet alone can lead to remission of the pulmonary symptoms.

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Check for updates

Pachydermodactyly

Paquidermodactilia

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A 14-year-old boy with a history of atopy went to the dermatologist with a history of progressive painless swelling of the fingers on both hands in the last two years. Manifestations of systemic or mental disorders were excluded. Examination revealed a symmetrical pattern of fusiform thickening of the proximal interphalangeal joints and dry skin around interdigital areas of the hands (Fig. 1). Imaging showed increased fibrosis without signs of synovitis or collections (Fig. 2 and 3). The patient was diagnosed of pachydermodactyly. Hydration of the hands was recommended and a

wait-and-see approach was decided on. Five months later the skin was hydrated and a slight regression was noticed.

Pachydermodactyly was first described in 1973 by Bazex, et al. and named by Verbov in 1975: pachy – thick, dermos – skin, dactylos – fingers[1].

It is a rare and benign form of acquired superficial digital fibromatosis, characterized by asymptomatic, symmetrical, periarticular soft tissue swelling of the proximal interphalangeal joints. It predominantly affects adolescent males[1-4].

Figure 1. Fusiform swelling affecting the joints of the second through fourth fingers of both hands. Dry skin can be observed between the first, second and third fingers of the right hand and the third, fourth and fifth fingers of the left hand.

Figure 2. Radiography shows soft tissue swelling without structural involvement of the interphalangeal joints.

Figure 3. Magnetic resonance imaging (MRI) of the hands. On **A** the T1-weighted image shows a dark colored thickening around the proximal interphalangeal joints. On **B** the Proton Density image shows a gray sign in these thickened areas. This MRI confirms the increased fibrosis around the joints without signs of edema, synovitis or collections.

The etiology is unknown, but repetitive local trauma or compulsive habits of interlacing or rubbing the fingers may contribute[2]. Pruritus is a precipitating factor[3]. It has been reported in patients with anxiety and obsessive-compulsive disorders[2].

Diagnosis is essentially clinical. It must be differentiated from inflammatory arthritis (associated with joint pain, limitation of joint movement and morning stiffness); knuckle pads (that affect the dorsal rather than lateral surfaces of the fingers); and pachydermoperiostosis (associated with digital clubbing)[3].

Laboratory tests are usually unnecessary[3]. Imaging typically reveals soft tissue swelling without structural involvement of the interphalangeal joints[2].

Treatment is needless apart from avoidance of mechanical stimulation[3]. Intralesional glucocorticoids and surgery could be used in specific cases[4]. When associated with mental disorders, psychiatric referral must be considered[2].

Recognition of this condition and a correct differential diagnosis is important in order to avoid invasive exams and anti-inflammatory or immunosuppressive treatments.

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Conflicts of interest

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Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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Rare etiology of maculopapular rash

Etiologia rara de exantema maculopapular

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Keypoints

What is known

– Pityriasis rubra pilaris is a rare inflammatory dermatosis with unknown etiology.

– It can present in any age, being more common at 6 to 7 years of age and fifth to sixth decade of life. The incidence is unknown, appearing to be similar in both females and males.

– It usually presents has a cephalocaudal hyperkeratotic scaly-erythematous maculopapular rash that progresses to a generalized erythroderma with islands of sparing.

What is added

– Due to its rarity, a high index of suspicion is needed. It should be suspected in the presence of maculopapular hyperkeratotic rashes with erythroderma.

– Although spontaneous remission can occur, PPR usually persists for several years, having a significant impact on quality of life.

A sixteen-year-old boy, with history of a suspected cutaneous antibiotic adverse reaction, was admitted to the emergency department due to a 10 day evolution pruriginous scaly-erythematous maculopapular rash. The lesions appeared on face with caudal progression. He was treated on the third day with oral and topical corticosteroid and oral antihistamine. On the sixth day, he initiated cough and, on the ninth day, fever. Three weeks earlier, he had an upper airway infection medicated with a mucolytic agent (ambroxol), paracetamol and nasal phenylephrine. Ingestion of other drugs was denied.

Physical examination revealed exuberant erythematous and coalescing maculopapules on face, trunk, perineum and limbs, lip fissures and tonsillar hyperemia (Figs. 1-3). Laboratory workup revealed normal hemoleucogram, normal kidney and liver function, CRP 20.1mg/L and negative serological testing for CMV, HIV, EBV, parvovirus B19 and mycoplasma. Paul-Bunnell reaction, antistreptolysin O titer, group A Streptococcus rapid antigen detection test and throat culture were also negative. Herpes simplex virus I/II IgM antibody was negative and IgG was inconclusive. The previous treatment with ambroxol and paracetamol led to toxicodermia suspicion. The case was discussed with Dermatology and he was started on hydroxyzine and prednisolone with mild erythema improvement but with the appearance of new lesions. Because of the scarlatinous appearance of the lesions, a single dose of intramuscular penicillin was administered, without any improvement. A skin biopsy was then performed and the patient was discharged to Dermatology

Figure 1. Clinical image showing exuberant scaly-erythematous maculopapular rash on face and trunk.

Figure 2. Clinical image showing scaly maculopapular rash on trunk, sparing the hands.

Figure 3. Clinical image showing marked scaly lesions.

consultation on weaning prednisolone. The skin biopsy results revealed pityriasis rubra pilaris (PRP) and the patient initiated systemic isotretinoin for 16 months with improvement, but with persistence of desquamation and pruritus. Three years later, a tenuous erythema remains along with keratoderma and desquamation.

PRP is a rare idiopathic inflammatory dermatosis that typically presents as cephalocaudal follicular hyperkeratotic papules that progress to a generalized erythroderma with islands of sparing. Most cases are sporadic, but some (< 5%) have autosomal dominant transmission[1-3]. Familial cases have been linked to gain of function mutations in the caspase recruitment domain family member 14 (CARD14 gene), leading to nuclear factor-kB activation and cutaneous inflammation[1]. Drug induced PRP has also been described, being tyrosine kinase inhibitors and phosphoinositide 3-kinase inhibitors the most frequently reported. It was classified by Griffiths into 5 subtypes: type I-classical adult, type II-atypical adult, type III-classical juvenile, type IV-circumscribed, type V-atypical juvenile. Recently, type VI-HIV associated PRP was added[1,2].

Circumscribed PRP is the most common type in children. Due to its rarity, a high index of suspicion is needed. The diagnosis is based on clinical and histopathological findings[1-3]. There is no treatment consensus[1-4]. The first line therapies are topical emollient,

keratolytic agents and systemic retinoids. Methotrexate, phototherapy and biologic IL-17 or IL-23 inhibitor are also effective[1,2,4]. Although spontaneous remission can occur, PPR usually persists for several years, having a significant impact on quality of life.

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None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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Primary erythromelalgia: a clinical diagnosis

Eritromelalgia primária: um diagnóstico clínico

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Keypoints

What is known
– Erythromelalgia is a rare chronic disorder responsible for neuropathic pain in pediatric age.
– Its etiology can be genetic or secondary.
– There is no cure or universally effective therapies.

What is added
– Awareness about erythromelalgia as a possible cause of neuropathic pain in children is important for its prompt diagnosis.
– Due to the impact on quality of life, its early identification is essential.

Erythromelalgia is a rare chronic disorder characterized by a triad of intermittently red, hot and painful extremities. The syndrome usually affects the lower extremities with symmetrical cutaneous findings, but may also involve the upper extremities and, rarely, the face and present with unilateral involvement only. These episodes can last from minutes to days and are characteristically aggravated by warming and relieved by cooling measures. The condition can be classified as primary or secondary, depending on the detection of an underlying cause. Multiple disorders can be linked to erythromelalgia, but special attention should be given to myeloproliferative illnesses, responsible for about 10 percent of secondary cases. Up to the present time, there is no cure or universally effective therapies[1,2].

We report a case of a previously healthy 19-month-old male child referred to a pediatric appointment for recurrent episodes of erythema, heat, edema and pain in the lower limbs, which endured for one to two hours, triggered by defecation or local trauma and relieved by immersion of the extremities in cold water. These episodes had been occurring in a monthly matter for seven months. His mother brought photographs that evidenced the complaints (Figs. 1 and 2). He had no other associated symptoms or signs, his physical examination was normal and laboratorial evaluation excluded secondary causes. There was family history of similar episodes in the maternal branch, without an established diagnosis. In view of the suspicion of primary familial erythromelalgia, a directed genetic study was performed, which showed a mutation in the *SCN9A* gene, confirming the diagnosis. Regarding the association of the child's symptoms to defecation effort, a laxative therapeutic was started and topical lidocaine was prescribed for acute relief. To date, more sparse intermittent episodes keep occurring, without significant daily functioning compromise.

Primary erythromelalgia is associated with a mutation in the *SCN9A* gene, which encodes an aberrant ion channel responsible for the hyperexcitability of peripheral nociceptors. This mutation can be sporadic or familial, being transmitted as an autosomal dominant trait.

Figure 1. Child with erythematous right lower limb.

Figure 2. Child with erythematous and swollen right lower limb.

Diagnosis is clinical, genetically confirmed[3]. Treatment is based on behavioral measures, such as avoiding precipitating factors and body cooling measures, and pain-modulation pharmacological therapies. Ice-cold water immersion can attain instant relief, but it also can lead to severe complications, such as skin ulcers and necrosis. Pharmacological intervention with topical anesthetics or oral agents for neuropathic pain may also be used, but pediatric data is still limited. Due to the impact on quality of life, its early identification is essential[1,2,4].

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Localized hypertrichosis after meningococcal B vaccine

Hipertricose localizada após vacina meningocócica B

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Keypoints

What is known
– Bexsero® vaccine is used to confer protection against meningococcal disease.
– There are several well-recognized and reported side effects in the brochure such as are pain at the injection site, swelling, induration, erythema, general malaise.
– The exact mechanism underlying this phenomenon, acquired localized hypertrichosis, is unknown.

What is added
– We find interesting and original, that there are only one case described.
– So this case is raising the attention to a possible and a rare side effect with Bexsero®, that all general practitioners and pediatricians should be aware of.
– This side effect was not reported yet in the brochure of this vaccine.

Vaccination is the most effective measure to prevent meningococcal disease. Bexsero® vaccine is used to confer protection against this disease caused by *Neisseria meningitidis* of group B. It was included in the National Vaccination Program in Portugal since October of 2020. The planned scheme is the administration of 3 doses at 2, 4 and 12 months. The adverse reactions to this vaccine reported are pain at the injection site, swelling, induration, erythema, general malaise, myalgias, arthralgias, headache and vomiting.

A 4 months old female, born in Portugal, came to the program surveillance consultation with a focal area of hair growth about 1cm x 1 cm localized on the antero-lateral side of the left thigh where Bexsero® vaccine was inoculated (Fig. 1). According to the mother, this increased hair growth developed approximately 2 weeks after vaccine administration at 2 months.

There was no documented history of local trauma, topical applications, or any other oral or injectable drug administered to the child. At birth, she received one dose of Hepatitis B vaccine intramuscularly, without documented side effects.

Hypertrichosis is characterized by increased hair growth independent of androgen excess. Acquired localized hypertrichosis is rarely reported at vaccination sites. The exact mechanism underlying this phenomenon is unknown, but probably is associated with aluminium adsorbed vaccines. It also has been suggested that prolonged exposure to antigen results in the production of cytokines that can affect nonimmune system cells such as hair follicles and promote localized hair growth.

This adverse reaction was reported to the National Authority for Medicines and Health Products in Portugal
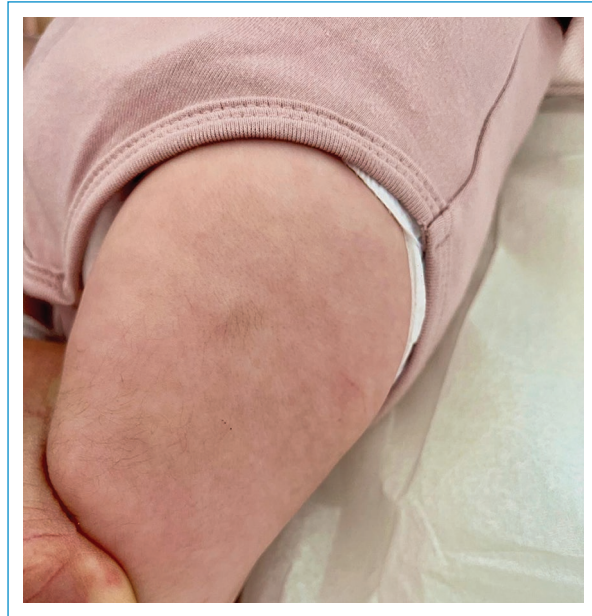
Figure 1. A focal area of hypertrichosis about 1 cm × 1 cm localized over the anterolateral side of the left thigh.

Ethical disclosures

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(INFARMED) and was registered in the database of the National Pharmacovigilance System. Since this clinical event occurred with an acceptable temporal relationship and the causal link with concomitant diseases or other drugs is unlikely, it was described for the first time as probable causality.

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