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Original article

Enteral feeding in preterm newborns – determinants of progression

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Abstract

Background: Delay in achieving full enteral feeding (FEF) in preterm newborns is associated with longer hospital stays and greater comorbidities.

Methods: Medical records review of newborns with gestational age ≤ 32 weeks, born between July 2014 and June 2020.

Results: 219 patients included, median gestational age – 31 weeks, median birth weight – 1,353 grams. 97% started enteral feeding (EF) in the first 72 hours of life. Substrates used were human milk in 27%, premature formula in 29% and mixed feeding in 49%. Median time of minimal EF – 3 days and to achieve FEF – 7 days. 69% of patients used parenteral nutrition (median time – 8 days). Median central line time – 8 days. Late-onset sepsis, apnea of prematurity, persistent ductus arteriosus, red blood cells transfusion and ventilatory support were associated with a longer time to achieve FEF.

Conclusion: Our patients introduced EF within the recommended timeline, and early introduction was not associated with necrotizing enterocolitis or difficulties in enteral progression (EP). We reported less time to achieve FEF than other studies. Despite the fact that exclusive human milk was used by a minority of patients, we report higher numbers than other studies. Surprisingly the type of substrate had no impact on EP. Difficulties in EP happened in a minority of patients, and the main cause was feeding intolerance. Severely ill infants took a longer time to achieve FEF. It is important to create guidelines to minimize variability between Units.

Keywords

Central catheter, enteral feeding, feeding intolerance, necrotizing enterocolitis, parenteral nutrition, preterm.

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Introduction

Premature newborns have higher nutritional needs in the neonatal period than in any other period of their lives because of their physiological immaturity and comorbidities that increase metabolic needs like sepsis, surgery, acidosis, hypotension, hypoxia and others [1].

Adequate and early nutritional support is crucial to have a good growth rate and to improve neurodevelopment outcomes [1, 2]. However, post-natal growth restriction is still a problem in Neonatal Intensive Care Units (NICUs), and one of the reasons is inadequate nutrition [3, 4].

On the one hand, intensive feeding strategies can have some associated risks like feeding intolerance or necrotizing enterocolitis (NEC) [1]. On the other hand, delay in achieving full enteral feeding (FEF) is associated with a longer time of parenteral nutrition (PN) and the use of central line that leads to greater morbidity [2].

There is great variability between NICUs on providing enteral feeding (EF) during the neonatal period, and it is a challenge to feed these infants [2, 3, 5].

Reduction of variability in NICU practices concerning EF leads to better outcomes, and the existence of guidelines improves mortality and morbidity and leads to faster achievement of FEF and better post-natal growth [3, 5].

The purpose of this study was to characterize EF in our NICU and evaluate what clinical features impact its progression.

Material and methods

This is a retrospective, descriptive study based on medical records review of preterm newborns with gestational age ≤ 32 weeks, hospitalized in the NICU of Hospital da Senhora da Oliveira de Guimarães and born between July 2014 and June 2020. We obtained a total number of 219 patients that fit these criteria. There were no exclusion criteria.

The following variables were collected: gender, birth weight, gestational age, prenatal pathology, maternal pathology, timing of introduction of EF, type of substrate used during enteral progression (EP), duration of minimal EF, use and duration of PN, suspension of EF, newborn comorbidities, type of ventilation, use and duration of central catheters, difficulties in EP, achievement of FEF.

Minimal EF was defined by EF < 25 mL/kg/day; achievement of FEF was considered when the newborn received total fluid intake only by the enteral route. Patients who had to suspend EF during EF were considered to have difficulties in EP. Neonatal sepsis was considered when the newborn had a positive blood culture, and clinical or laboratory finds compatible with sepsis. Fetus with abdominal circumference < P10 or estimated fetal weight < P10 and impaired diastolic velocity of the umbilical artery were considered to have intrauterine growth restriction. NEC was defined and classified according to the "Modified Bell Staging System" [6].

Data collection and statistical analysis were performed using IBM® SPSS® Statistics 26. Categorical variables were characterized by absolute and relative frequencies and continuous variables by median and interquartile range. To compare different variables with difficulties in EP, the Mann-Whitney U test was used for continuous variables and the Chi-squared test for categorical variables. Correlation between continuous variables and time to achieve FEF was calculated by the Spearman correlation test. A p-value inferior to 0.05 was considered statistically significant.

Results

In the present cohort of 219 preterm infants, 61% were male (n = 134), median gestational age was 31 weeks (P25 – 28; P75 – 32 weeks), and median birth weight was 1,353 grams (P25 – 1,090; P75 – 1,675 grams).

Clinical characteristics of patients are presented in **Tab. 1**. **Tab. 2** shows the characteristics of EF and PN.

Almost all patients (97%, n = 212) started EF within the first 3 days of life. Causes for delay of EF in the remaining 3% were gastrointestinal bleeding (n = 1), presence of biliary or hematic gastric residues (n = 2), respiratory distress (n = 2) and absence of human

Table 1. Clinical characteristics of patients.

Characteristics		n (%)
Gender	Male	134 (61%)
	Female	85 (39%)
Prenatal pathology	Infectious risk	148 (68%)
	Intrauterine growth restriction	35 (16%)
Maternal pathology	Pre-eclampsia	14 (6%)
	Trombocytopenia	5 (2%)
	Gestational diabetes	20 (9%)
Type of ventilation	Invasive mechanical ventilation	43 (20%)
	CPAP	200 (91%)
	Bilevel CPAP	26 (12%)
	High-flow nasal cannula	50 (23%)
Red globules transfusion	Yes	43 (20%)
	No	176 (80%)
Newborn comorbidites	Early-onset sepsis	30 (14%)
	Late-onset sepsis	30 (14%)
	Pneumothorax	12 (6%)
	PDA needing treatment	14 (11%)
	Apnea of prematurity	84 (38%)
	Infant respiratory distress syndrome	162 (74%)
	NEC treated with surgery	3 (1%)
	NEC treated only with antibiotics	4 (2%)

CPAP: continuous positive airway pressure; NEC: necrotizing enterocolitis; PDA: persistent ductus arteriosus.

Table 2. Characteristics of enteral feeding (EF) and parenteral nutrition (PN).

Characteristics		n (%)		
Timing of introduction of EF	< 24 hours of life	96 (44%)		
	24-72 hours of life	116 (53%)		
	> 72 hours of life	7 (3%)		
Substrate for EP	Human milk	48 (27%)		
	Preterm formula	42 (29%)		
	Mixed feeding	86 (49%)		
Use of PN	Yes	151 (69%)		
	No	68 (31%)		
Difficulties in EP	Yes	47 (21%)		
	No	172 (79%)		
Characteristics		**Median**	**P25**	**P75**
Time of minimal EF (days)		3	3	4
Time of PN (days)		8	6	10
Time to achieve FEF (days)		7	5	10

EF: enteral feeding; EP: enteral progression; FEF: full enteral feeding; PN: parenteral nutrition.

milk (n = 2). A minority of patients had difficulties with EP (21%, n = 47; **Fig. 1**).

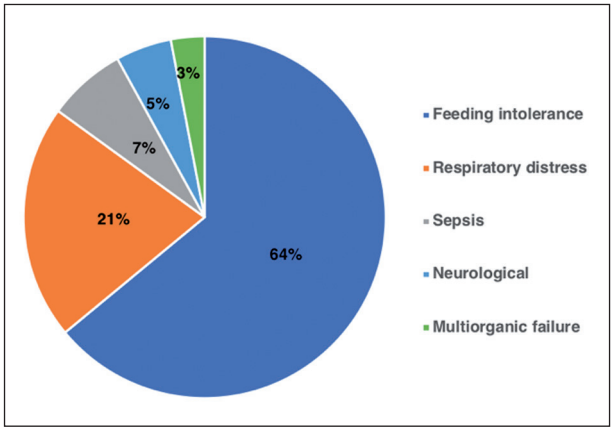

Figure 1. Causes of difficulties in enteral progression (EP).

The majority of infants had a central venous catheter (63%, n = 138) and the median time was 8 days (P25 – 6; P75 – 11 days); 37% of patients had an umbilical arterial catheter (n = 80) for a median time of 2 days (P25 – 1; P75 – 2 days).

Patients with late-onset sepsis, pneumothorax, NEC, persistent ductus arteriosus (PDA) needing treatment, invasive mechanical ventilation and red blood cells transfusion had more difficulties with EP (**Tab. 3**).

Seven infants (3%) were diagnosed with NEC. All of them started EF within the first 3 days of life; there were no statistically significant differences between starting EF early or late associated with NEC diagnosis (p = 1). Duration of minimal EF was slightly higher in premature infants with NEC (median – 4 days) compared with those without NEC (median – 3 days); however, this difference was not statistically significant (p = 0.126).

The median time to achieve FEF was 7 days (P25 – 5; P75 – 10 days; **Tab. 2**). Newborns who introduced EF after 72 hours of life, who had late-onset sepsis, apnea of prematurity, PDA needing treatment, who needed invasive mechanical ventilation, a continuous positive airway pressure (CPAP) or had red blood cells transfusion took more time to achieve FEF; this difference has statistical significance (**Tab. 4**).

Patients with minimal EF for a longer time took a longer time to achieve FEF ($r = 0.53$, $p < 0.01$, **Fig. 2**). Newborns with lower birth weight and lower gestational age reached FEF later ($r = -0.411$, $p < 0.01$, and $r = -0.432$, $p < 0.01$, respectively). Patients who took a longer time to achieve FEF had PN and central venous catheter for a longer time ($r = 0.676$, $p < 0.01$, and $r = 0.618$, $p < 0.01$, respectively).

Table 3. Comparison between clinical characteristics and difficulties in enteral progression (EP).

		With difficulties in EP	Without difficulties in EP	
Characteristics		**Median**	**Median**	**p-value**
Gestational age (weeks)		28	31	**< 0.01**
Birth weight (grams)		1,047	1,425	**< 0.01**
Duration of minimal EF (days)		5	3	**< 0.01**
Duration of PN (days)		12	7	**< 0.01**
Characteristics		**n (%)**	**n (%)**	**p-value**
Gender	**Female**	15 (7%)	70 (32%)	0.647
	Male	27 (12%)	107 (49%)	
Infectious risk	**Yes**	30 (14%)	118 (54%)	0.553
	No	12 (6%)	59 (27%)	
Intrauterine growth restriction	**Yes**	6 (3%)	29 (13%)	0.739
	No	36 (16%)	148 (68%)	
Maternal pre-eclampsia	**Yes**	3 (1%)	11 (5%)	0.735
	No	36 (16%)	166 (76%)	
Gestational diabetes	**Yes**	2 (1%)	18 (8%)	0.379
	No	40 (18%)	159 (73%)	
Maternal thrombocytopenia	**Yes**	0 (0%)	5 (2%)	0.586
	No	42 (19%)	172 (79%)	
Type of substrate	**Exclusive human milk**	12 (5%)	36 (16%)	0.501
	Preterm formula or mixed feeding	26 (12%)	102 (47%)	
Timing of introduction of EF	**Early (≤ 72 hours)**	40 (18%)	172 (79%)	0.622
	Late (> 72 hours)	2 (1%)	5 (2%)	
Early-onset sepsis	**Yes**	9 (4%)	21 (10%)	0.105
	No	33 (15%)	156 (71%)	
Late-onset sepsis	**Yes**	19 (9%)	11 (5%)	**< 0.01**
	No	23 (11%)	166 (76%)	
Pneumothorax	**Yes**	7 (3%)	5 (2%)	**< 0.01**
	No	35 (16%)	172 (79%)	
Apnea of prematurity	**Yes**	20 (9%)	64 (29%)	0.170
	No	22 (10%)	113 (52%)	
Infant respiratory distress syndrome	**Yes**	36 (16%)	46 (21%)	0.644
	No	11 (5%)	126 (57%)	
NEC	**Yes**	7 (3%)	0 (0%)	**< 0.01**
	No	34 (16%)	177 (81%)	
PDA needing treatment	**Yes**	10 (5%)	14 (6%)	**0.01**
	No	32 (15%)	163 (74%)	
Invasive mechanical ventilation	**Yes**	25 (11%)	17 (8%)	**< 0.01**
	No	18 (8%)	159 (73%)	
CPAP	**Yes**	39 (18%)	161 (74%)	0.695
	No	3 (1%)	16 (7%)	
Bilevel CPAP	**Yes**	14 (6%)	12 (6%)	**< 0.01**
	No	28 (13%)	165 (75%)	
High-flow nasal cannula	**Yes**	12 (6%)	38 (17%)	0.324
	No	30 (14%)	139 (63%)	
Red blood cells transfusion	**Yes**	23 (11%)	20 (9%)	**< 0.01**
	No	19 (9%)	157 (72%)	

CPAP: continuous positive airway pressure; EF: enteral feeding; EP: enteral progression; NEC: necrotizing enterocolitis; PDA: persistence of ductus arteriosus; PN: parenteral nutrition.

Table 4. Comparison between clinical characteristics and time to achieve full enteral feeding (FEF).

Characteristics		Time to achieve FEF		p-value
		Median	P25-P75	
Gender	**Female**	7	6-10	0.707
	Male	7	4-10	
Infectious risk	**Yes**	7	5-10	0.170
	No	8	5-11	
Intrauterine growth restriction	**Yes**	9	6-11	0.140
	No	7	5-10	
Maternal pre-eclampsia	**Yes**	10	8-13	0.234
	No	7	5-10	
Gestational diabetes	**Yes**	8	5-11	0.556
	No	7	5-10	
Type of substrate	**Exclusive human milk**	9	7-12	0.151
	Preterm formula or mixed feeding	7	5-10	
Timing of introduction of EF	**Early (≤ 72 hours)**	7	5-10	**< 0.01**
	Late (> 72 hours)	16	10-29	
Early-onset sepsis	**Yes**	9	5-12	0.189
	No	7	5-10	
Late-onset sepsis	**Yes**	14	8-18	**< 0.01**
	No	7	5-10	
Pneumothorax	**Yes**	9	0-17	0.754
	No	7	5-10	
Apnea of prematurity	**Yes**	8	6-11	**0.042**
	No	7	4-10	
Infant respiratory distress syndrome	**Yes**	8	5-11	0.123
	No	6	4-9	
NEC	**Yes**	6	5-15	0.559
	No	7	5-10	
PDA needing treatment	**Yes**	11	8-16	**< 0.01**
	No	7	5-10	
Invasive mechanical ventilation	**Yes**	10	4-15	**0.024**
	No	7	5-10	
CPAP	**Yes**	7	5-10	**< 0.01**
	No	4	3-8	
Bilevel CPAP	**Yes**	15	9-20	**< 0.01**
	No	7	5-10	
High-flow nasal cannula	**Yes**	10	7-14	**< 0.01**
	No	6	4-9	
Red blood cells transfusion	**Yes**	12	6-17	**< 0.01**
	No	7	5-9	

CPAP: continuous positive airway pressure; EF: enteral feeding; FEF: full enteral feeding; NEC: necrotizing enterocolitis; PDA: persistence of ductus arteriosus.

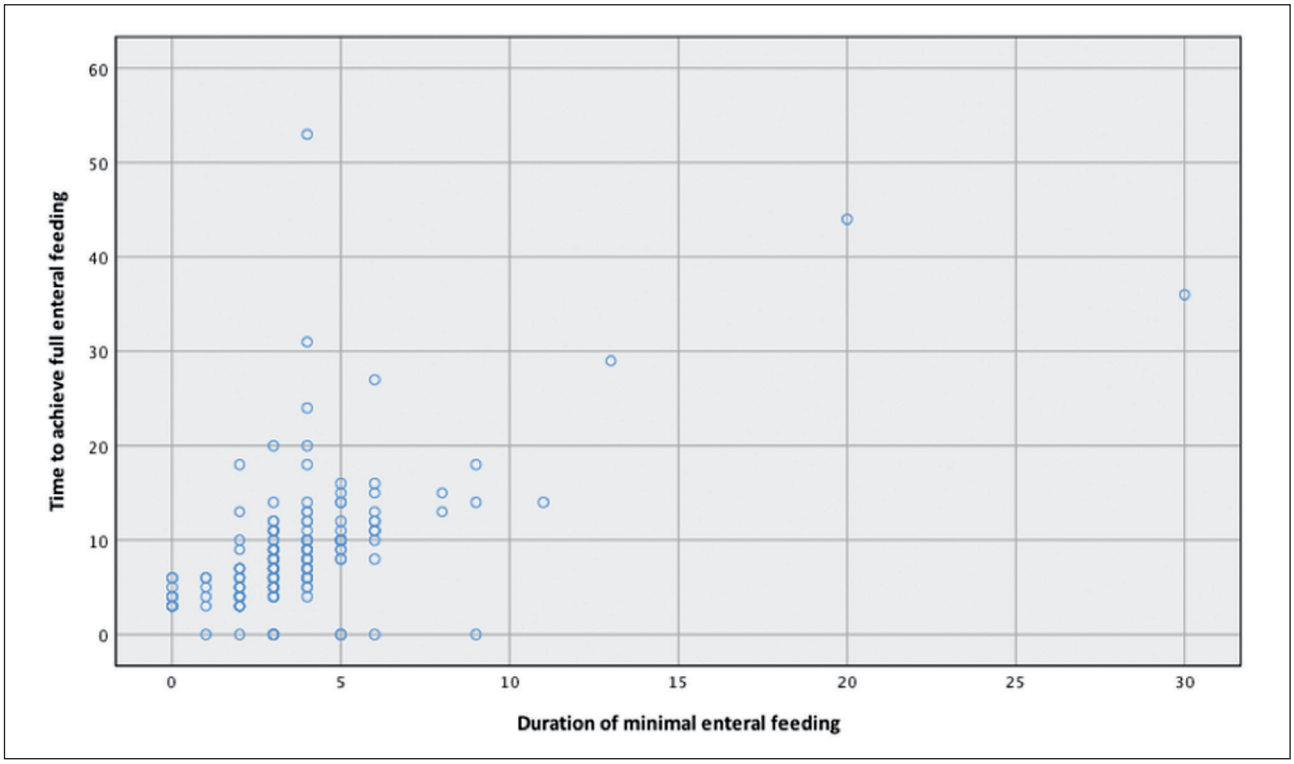

Figure 2. Correlation between time of minimal enteral feeding (EF) and achievement of full enteral feeding (FEF) ($r = 0.53$, $p < 0.01$).

Discussion

Even though there is no clear consensus in guidelines concerning EF, there are some reports that recommend early and progressive EF [7]. The exact time to introduce EF is not well defined, but it is recommended to initiate within the first 24 to 72 hours of life and, if possible, in the first 6 hours, if medically safe [1, 3]. In our study, almost half of our patients introduced EF on the first day, and almost all of them introduced EF before 3 days of life which goes according to current recommendations. The minority of premature infants that had to delay the beginning of EF had clinical reasons that justify this delay as described in the literature, mainly gastrointestinal and respiratory instability [5]. The timing of the introduction of EF was not associated with difficulties with EP; however, as it would be expected, newborns that started EF > 72 hours of life took a longer time to achieve FEF.

We verified that in our NICU about a third of patients had exclusive human milk; however, almost half of them had a mixed feeding with maternal milk and preterm formula. It is well established that the best way to start EF is with maternal milk; the second option is donor's milk, and the preterm formula is reserved for the last option [1, 3, 7]. In our NICU, donor's milk is not available, and sometimes in the first post-labor hours or days it is difficult for the mother to express milk. These can explain why we have few premature infants doing exclusive breast milk. However, our numbers are higher than reported in other NICUs [7]. Surprisingly, when comparing exclusively breastfed newborns with those who had preterm formula or mixed feeding, we found no difference between the two groups and the achievement of FEF or the presence of difficulties in EP.

Guidelines recommend starting EF with trophic feeds for 1 to 3 days [3]. We reported a median time of minimal EF of 3 days, which goes according to these recommendations and also what is practiced in other NICUs [1]. Premature infants with NEC had a slightly higher duration of minimal EF; however, this difference was not significant.

In our study, we reported less time to achieve FEF than other reports [2, 7, 8]. This difference manifests the variability of guidelines and feeding protocols between NICUs. This can also be explained by the fact that those reports had a more conservative approach than in our Unit.

As it would be expected because of gastrointestinal prematurity, the majority of our newborns used PN. Median days of PN were the same as days of central lines and also similar to the median days to achieve FEF. In other NICUs, central catheters are removed

when patients achieve an EF of 100 mL/kg/day [1]. This is not a practice in our Unit. This approach may lead to fewer days of PN and central line, which could translate to fewer complications like sepsis or cholestasis. Even so, we reported fewer days of PN than other studies [7]. Patients who needed longer time to achieve FEF and who had difficulties in EP had a longer time of PN and central catheter, with higher rates of late-onset sepsis.

Difficulties in EP happened in a minority of patients, and the main cause was feeding intolerance. Feeding intolerance is very common in preterm infants, and it happens in 29% of cases. This can translate the immaturity of the gastrointestinal tract, which is strictly related to gestational age [9]. We also observed in our study that patients with lower birth weight and lower gestational age had more difficulties in EP and took more time to achieve FEF. Prematurity and low birth weight are associated with more comorbidities that can influence EF. In fact, we reported that premature infants who were severely ill with sepsis, pneumothorax, NEC, who needed treatment for PDA, ventilatory support or red blood cells transfusion had more problems in EP.

Gender, maternal or prenatal pathology were not associated with more difficulties in EP or more time to achieve FEF.

There were some limitations in our study. Being a retrospective study based on medical records sometimes leads to missing data. We were not able to have a better definition for FEF because data was lacking on patients' records, which can lead to difficulties comparing it with other centers.

Conclusions

The majority of our patients introduced EF early, and we verified that our patients took less time to achieve FEF than other studies. Feeding intolerance is very common between Units and was the major cause of EP difficulties in our population. Gestational age, birth weight and post-natal comorbidities have more impact on EF and EP than maternal pathology or prenatal disease. Surprisingly, the type of substrate has no impact on EP or achievement of FEF, and the timing of introduction of EF has no impact on EP. It is important to minimize variability between Units and to create guidelines that lead to a decrease in morbidity and mortality. With this study, we were able to verify our current approach to EF, helping us define strategies and guidelines to improve this feature in the future.

Declaration of interest

The Authors declare no conflict of interests. No funding was secured for this study.

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