Enteral Feeding and Necrotizing Enterocolitis: Does Time of First Feeds and Rate of Advancement Matter?

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ABSTRACT

Objective: The aim of the study was to determine if time to initial enteral feeding (EF) and rate of advancement are associated with necrotizing enterocolitis (NEC) or death.

Methods: Secondary analysis of prospectively collected data of very-low-birth-weight infants (VLBWI: 400–1500 g) born in 26 NEOCOSUR centers between 2000 and 2014.

Results: Among 12,387 VLBWI, 83.7% survived without NEC, 6.6% developed NEC and survived, and 9.6% had NEC and died or died without NEC (NEC/death). After risk adjustment, time to initial EF (median = 2 days) was not associated with NEC; however, delaying it was protective for NEC/death (odds ratio [OR] = 0.96; 95% confidence interval [CI] 0.93–0.99). A slower feeding advancement rate (FAR) was protective for NEC (OR = 0.97; 95% CI = 0.94–0.98) and for NEC/death (OR = 0.98; 95% CI = 0.96–0.99).

Conclusions: In VLBWI, there was no association between an early initial EF and NEC, although delaying it was associated with less NEC/death. A slower FAR was associated with lower risk of both outcomes.

Key Words: enteral nutrition, feeding practices, premature infant, very-low-birth-weight infant

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What Is Known

- Necrotizing enterocolitis is a common serious complication in very-low-birth-weight infants.
- Feeding practices may have a role on its occurrence but the optimal feeding strategy for the most immature infants remains unclear.

What Is New

- Early feeding of very-low-birth-weight infants does not increase the risk of necrotizing enterocolitis.
- A slower feeding advancement rate in very-low-birth-weight infants was protective for necrotizing enterocolitis and the combined necrotizing enterocolitis/death outcome after risk adjustment.
- Other risk factors are more relevant in necrotizing enterocolitis than feeding practices, in particular gestational age, birth weight, male sex, mechanical ventilation, and severe intraventricular hemorrhage.

Necrotizing enterocolitis (NEC) is a severe inflammatory process of the intestines that affects predominantly premature newborns. It remains one of the main causes of morbidity and mortality in very-low-birth-weight infants (VLBWI) and continues to be the main surgical emergency in the neonatal intensive care unit (NICU). Large, multicenter, neonatal network databases from different world regions show that the prevalence of NEC in VLBWI has remained stable during the last decades, ranging from 7% to 10% (1–7). Overall mortality of patients with NEC ranges between 10% and 50%, with the highest rates among more immature infants and those who require surgery (8–10).

NEC pathogenesis is complex and multifactorial. Key elements in its development include intestinal immaturity, local inflammatory response, ischemia, and altered intestinal microbiota. Thus, the NICU constitutes a risk environment in which enteral feeding (EF) might play a crucial role (1,2,6,7,11–13). NEC affects mainly preterm infants (mostly those of lower gestation) who have survived beyond the first days of life and have started EF. On the basis of the existing evidence, the most appropriate time to start EF and the rate of advancement remain unclear (14,15).

The present study was aimed to determine if time to initial EF and feeding advancement rate (FAR) were associated with NEC or the composite NEC/death as an outcome, after adjusting by known perinatal risk variables.

MATERIALS AND METHODS

Study Population

The NEOCOSUR Neonatal Network is a South American cooperative, nonprofit association established in 1997 to monitor VLBWI in the region (www.neocosur.org). Presently, it includes 32 tertiary neonatal centers in Argentina, Brazil, Chile, Paraguay, Peru, and Uruguay. NEOCOSUR prospectively registers data on all

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The names of the members of Neocosur Neonatal Collaborative Network are listed in the Supplementary Appendix: *http://links.lww.com/MPG/C230*.

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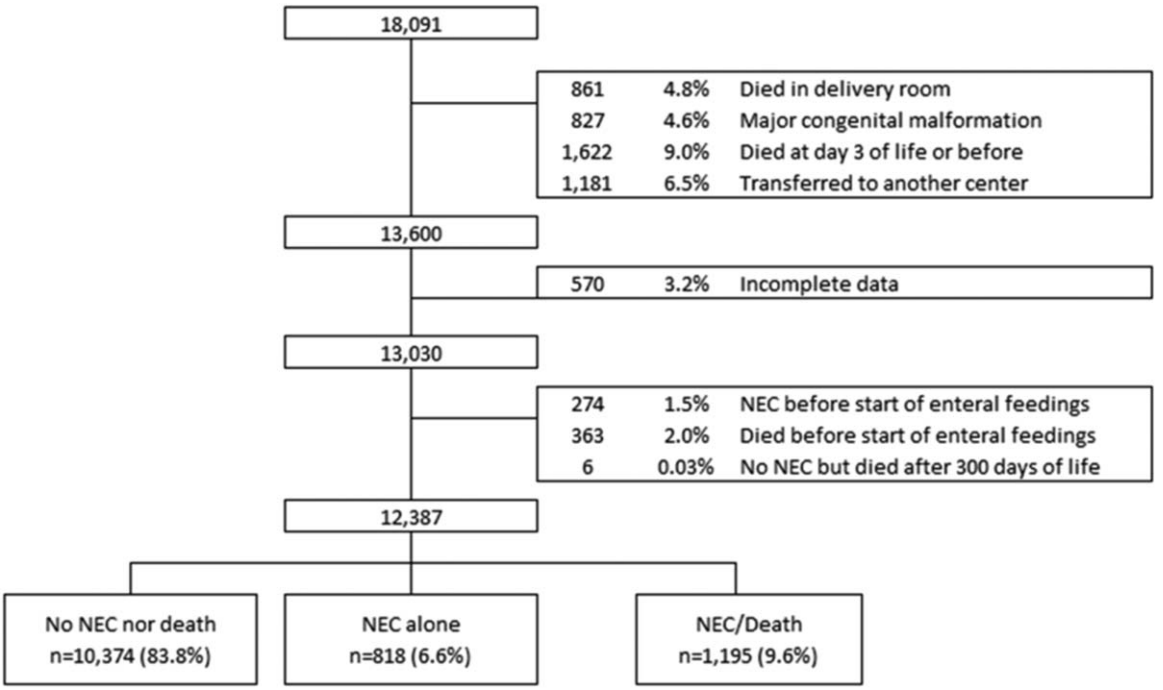

FIGURE 1. Population selection flowchart. 2001 to 2014, Neocosur Neonatal Network. NEC = necrotizing enterocolitis.

livebirth VLBWI whose birth weights (BWs) range from 400 to 1500 g, and are born in participating centers. It uses predefined diagnostic criteria and an online registry system.

Inclusion criteria for the present study were all live-born infants 400 to 1500 g at Neocosur centers between years 2001 and 2014 (26 centers within this period), who survived beyond day 3 of life. Exclusion criteria for the study were infants who had major congenital malformations, were transferred to another center, presented with NEC or died before initiating EF, or had missing information relevant to the study (Fig. 1). The rationale for selecting infants surviving beyond day 3 of life and excluding those who presented with NEC or died before initiating EF was based on the aim in this study: to explore the association between feeding practices and NEC incidence.

Newborns were classified using 2 criteria: type of outcome and timing of outcome. There were 3 categories for type of outcome: ''no NEC nor Death''—composed by subjects who did not develop NEC nor died, ''NEC alone''—composed by infants who only developed NEC and survived, and ''NEC/death''—composed by those who developed NEC and died and those who died without having NEC. When considering timing of outcomes, newborns were classified in 3 groups: no NEC nor death, NEC or death (either or both) between initial EF and reaching 100 mL kg^{-1} day^{-1} (EF-100), and NEC or death after reaching EF-100.

Variables Analyzed

The following perinatal and postnatal variables affecting NEC prevalence were analyzed: exposure to antenatal steroids (ANS), premature rupture of membranes (PROM) of more than 18 hours, mode of delivery, gestational age (GA) (best obstetrical estimate), sex, BW and length, condition of small-for-gestational age (SGA), 1 and 5 minutes APGAR score $\leq$3, use of surfactant, use of mechanical ventilation, persistent ductus arteriosus (PDA) requiring treatment, severe (grade III or IV) intraventricular hemorrhage (sIVH), early-onset sepsis (EOS), late-onset sepsis (LOS) occurring before development of NEC and use of postnatal steroids. The diagnosis of NEC was considered when grade IIa Bell modified criteria or greater was reached (16). SGA was defined by Fenton curves (17). Severe intracranial hemorrhage (sIVH) was defined according to Papile (18). EOS was defined by positive blood culture before 72 hours of life and LOS by positive blood culture after 72 hours of life.

Statistical Methods

Descriptive analysis was done by group (no NEC nor death, NEC alone, NEC/death). Numerical variables were described using mean and standard deviation and categorical variables using percentages. One-way analysis of variance (ANOVA) test was used to compare means, and chi-square test to compare proportions among these groups. To test pair differences, multiple comparison tests were performed using Bonferroni correction.

Time to initial EF (each additional day in delaying EF) and time elapsed between initial EF and EF-100 (each additional day in reaching 100 mL/kg) were described using median and first and third quartiles (Q1 and Q3, respectively) among groups and subdividing these by timing of the event.

We also performed multivariate analyses using multinomial logistic regression, where groups according to type of outcome entered the regression as the dependent variable; ''no NEC nor death'' was set as the reference level. Time to initial EF was considered among explanatory variables. Adjustments for possible confounding variables were made including GA at birth, BW (per every 100 additional grams), birth length (cm), male sex, 1 minute APGAR score $\leq$3, 5 minutes APGAR score $\leq$3, antenatal steroid use, surfactant use, mechanical ventilation use, PDA requiring treatment, sIVH, EOS, LOS before NEC/death, postnatal steroids, C-section mode of delivery, PROM >18 hours, and SGA. When considering the effect of FAR on the type of outcome, age at initial

TABLE 1. Neonatal characteristics*

	Neither NEC nor death, n = 10,374	NEC alone, n = 818	NEC/death, n = 1195	*P* value
Gestational age, weeks, mean ± SD	29.7 ± 2.5	28.8 ± 2.6	27.0 ± 2.6	<0.001†,‡,§
Weight, g, mean ± SD	1175.7 ± 237.0	1064.7 ± 248.1	881.7 ± 241.5	<0.001†,‡,§
Length, cm, mean ± SD	37.2 ± 2.9	36.1 ± 3.0	34.0 ± 3.3	<0.001†,‡,§
Male sex, %	48.6	53.4	55.5	<0.001†,‡
Apgar 1 minute ≤3, %	12.4	14.1	30.5	<0.001‡,§
Apgar 5 minutes ≤3, %	1.1	1.8	5.5	<0.001‡,§
Use of prenatal steroids, %	82.1	80.7	72.7	<0.001‡,§
Use of surfactant, %	48.4	58.2	82.5	<0.001†,‡,§
PDA requiring treatment, %	24.8	35.3	44.4	<0.001†,‡,§
sIVH, %	4.7	9.3	32.0	<0.001†,‡,§
MV use, %	53.9	74.1	98.0	<0.001†,‡,§
Early-onset sepsis, %	2.4	2.5	5.6	<0.001‡,§
Late-onset sepsis previous of NEC/death, %	16.9	21.9	39.1	<0.001†,‡,§
Use of posnatal steroids, %	5.1	9.0	11.9	<0.001†,‡
Mode of delivery C-section, %	76.5	71.4	61.1	<0.001†,‡,§
PROM >18 hours, %	20.8	23.1	24.1	0.022‡
SGA, %	19.9	20.5	17.3	0.075

MV = mechanical ventilation; NEC = necrotizing enterocolitis; PROM = premature rupture of membranes; PDA = patent ductus arteriosus; sIVH = severe intracranial hemorrhage; SGA = small for gestational age (according to Fenton's curves).

*Neocosur Neonatal Network, 2001 to 2014.

†Significant difference between no NEC nor death and NEC alone (pairwise comparison [Bonferroni correction]).

‡Significant difference between no NEC nor death and NEC/death (pairwise comparison [Bonferroni correction]).

§Significant difference between NEC alone and NEC/death (pairwise comparison [Bonferroni correction]).

EF was added as explanatory variable along with previous variables considered as possible confounders.

For this analysis, the group that developed NEC between initial EF and EF-100 was excluded, as it is known that having NEC delays reaching full enteral nutrition. For both regressions, a stepwise procedure was undertaken to select a regression including only significant variables. Adjusted odds ratios (OR) and 95% confidence interval (CI) are shown to quantify the magnitude of the effect. Significance level was set at <0.05. Statistical analysis was performed using SPSS software (version 17.0, Inc, Chicago, IL). Figures were done using R software (version 3.5.0) (19).

Ethics

The School of Medicine's Research Ethics Committee at the Pontificia Universidad Católica de Chile assessed and approved the ethical considerations related to this study.

RESULTS

After considering inclusion/exclusion criteria, data from 12,387 babies were analyzed. Among these infants, 10,374 (83.8%) did not develop NEC nor died, 818 developed NEC alone (6.6%), and 1195 (9.6%) had NEC/death (Fig. 1).

When comparing baseline characteristics, multiple factors appear statistically significant, showing a difference between the no NEC nor death group and the NEC/death group; among them: gestational age (29.7 ± 2.5 vs 27 ± 2.6 weeks), use of antenatal steroids (82.1% vs 72.7%); BW (1,175 ± 237 vs 881.7 ± 241.5 g), male sex (48.6% vs 55.5%), 1 minute APGAR score ≤3 (12.4% vs 30.5%), surfactant use (48.4% vs 82.5%), mechanical ventilation (53.9% vs 98%), PDA treatment (24.8% vs 44.4%) and sIVH (4.7% vs 32%) (Table 1).

For all subjects included in the analysis, median age at initial EF was 2 days (Q1–Q3: 2–3) and median age at reaching EF-100 was 11 days (Q1–Q3: 8–16).

Analyses were made according to timing and type of outcome (Table 2). Comparisons were made between no NEC nor death group (as the reference group) and the other 4 sub-groups that result when combining timing and type of outcome. Although all groups showed similar median age at initial EF (2 days), significant differences were found in the distribution of initial EF between each sub-group and the no NEC nor death group, except for NEC alone after reaching EF-100. Regarding FAR, the no NEC nor death group reached EF-100 at a median age of 8 days, similar to NEC alone after reaching EF-100. The remaining groups reached EF-100 at a slower pace (*P* values <0.001), especially those who developed the event between initial EF and reaching EF-100.

Multivariate Analysis

For multivariate analysis of the effect of initial EF on the type of outcome (NEC alone or the composite outcome NEC/death), all newborns were included. After adjusting for possible confounders, the following variables appeared to be risk factors for the development of NEC alone: male sex (OR = 1.31, 95% CI = 1.10–1.55), mechanical ventilation (OR = 2.57, 95% CI = 1.98–3.34) and sIVH (OR = 1.41, 95% CI = 1.04–1.92). Two variables appeared to be protective for NEC: BW (each additional 100 g) (OR = 0.88, 95% CI = 0.81–0.94) and surfactant use (OR = 0.53, 95% CI = 0.42–0.68) (Fig. 2, left upper panel). For the composite outcome NEC/death, the following variables appeared to be risk factors: male sex (OR = 1.36, 95% CI = 1.15–1.62), mechanical ventilation (OR = 26.66, 95% CI = 14.87–47.79), sIVH (OR = 3.96, 95% CI = 3.21–4.87), LOS before outcome (OR = 1.36, 95% CI = 1.13–1.63) and SGA (OR = 1.51, 95% CI = 1.08–2.13). Variables that were protective for NEC/death were age in days at initial EF (OR = 0.96, 95% CI = 0.93– 0.99) gestational age (OR = 0.90, 95% CI = 0.84–0.96), BW (OR = 0.80, 95% CI = 0.74–0.86), antenatal steroids (OR = 0.66, 95% CI = 0.53–0.81), and surfactant use (OR = 0.58, 95% CI = 0.46–0.73) (Fig. 2, right upper panel).

TABLE 2. Age at initial enteral feeding and rate of advancement according to type of outcome*

	N		Age at start of enteral feeding (days)	Days between start of enteral feeds and reaching 100 mL kg^{-1} day^{-1}
No NEC nor death	10,374	Median (Q1–Q3) mean ± SD	2 (2–3) 2.86 ± 2.33	8 (6–11) 9.78 ± 6.62
NEC/death between start of enteral feeds and reach of 100 mL kg^{-1} day^{-1}				
NEC alone between start of enteral feeds and reach of 100 mL kg^{-1} day^{-1}	494	Median (Q1–Q3) mean ± SD	2 (2–4) 3.12 ± 2.87	23 (17–23) 27.27 ± 17.28
P value (ref: no NEC nor death)			*0.033*	*<0.001*
Both, NEC and death between start of enteral feeds and reach of 100 mL kg^{-1} day^{-1}	870	Median (Q1–Q3) mean ± SD	2 (2–4) 3.51 ± 3.07	25 (18–31.5) 28.84 ± 16.49
P value (ref: no NEC nor death)			*<0.001*	*<0.001*
NEC/death after reaching 100 mL kg^{-1} day^{-1}				
NEC alone after reaching 100 mL kg^{-1} day^{-1}	324	Median (Q1–Q3) mean ± SD	2 (2–4) 3.00 ± 2.28	8 (6–11) 9.71 ± 5.76
P value (ref: no NEC nor death)			0.112	0.277
Both, NEC and death after reaching 100 mL kg^{-1} day^{-1}	325	Median (Q1–Q3) mean ± SD	2 (2–4) 3.72 ± 3.57	9 (6–15) 11.97 ± 8.56
P value (ref: no NEC nor death)			*<0.001*	*<0.001*

P values obtained with Mann-Whitney *U*-test. NEC = necrotizing enterocolitis; Q1 = first quartile; Q3 = third quartile.
*Neocosur Neonatal Network, 2001 to 2014.

For multivariate analysis of FAR on the type of outcome, we included newborns who did not develop NEC nor died or developed the outcome after reaching EF-100. Those infants who developed the outcome before reaching EF-100 were excluded from this analysis because, as previously mentioned, infants with NEC are forced to withhold EF, and therefore achieving full enteral nutrition is delayed. For NEC alone, we found the following risk factors: mechanical ventilation (OR = 2.75, 95% CI = 1.86–4.06) and LOS before NEC (OR = 1.51, 95% CI = 1.11–2.07). Factors associated with lower risk of NEC were a slower FAR (each additional day in delay) (OR = 0.97, 95% CI = 0.94–0.99) and surfactant use (OR = 0.53, 95% CI = 0.37–0.75). For the composite outcome NEC/death, variables that appeared to be risk factors were mechanical ventilation (OR = 34.16, 95% CI = 14.53–80.35), sIVH (OR = 2.64, 95% CI = 1.83–3.81), LOS before NEC (OR = 2.14, 95% CI = 1.60–2.87) and postnatal steroids (OR = 1.94, 95% CI = 1.33–2.82). In agreement with the finding for NEC alone, a slower FAR was protective for the composite outcome NEC/death (OR = 0.98, 95% CI = 0.96–0.99). Other factors that appeared protective for NEC/death were BW (each additional 100 g) (OR = 0.79, 95% CI = 0.70–0.90) and surfactant use (OR = 0.39, 95% CI = 0.28–0.54) (Fig. 2, lower panels).

DISCUSSION

In this large population of VLBWI, after risk adjustment, we found no association between age of initial EF and the development of NEC, although an earlier initial EF was associated with an increased risk for NEC/death composite outcome. After adjusting for confounders, a slower FAR was protective for both outcomes: NEC alone and NEC/death (after reaching 100 mL/kg).

Although the optimal time of initial EF is still unclear, especially in the extremely immature infants, the most recent evidence does not associate early initial EF, started within the first 4 days of life, with NEC. A Cochrane meta-analysis shows that delayed feeding in infants <1500 g or <32 weeks does not affect NEC risk (RR: 0.93; 95% CI = 0.64–1.34; 8 studies, 1092 infants) (20). Studies have also examined the possible effect of trophic feeding versus enteral fasting in VLBWI. A meta-analysis of infants <1500 g suggests that the risk of NEC does not increase with trophic feeding (RR: 1.07; 95% CI = 0.67–1.70) (21). Our finding that early initial EF (mean = 2 days of life) was not associated with NEC agrees with those studies. We do not have a clear explanation for an increase in the risk of NEC/death with delaying initial EF, although this represents only about 1 day of difference and may not be clinically relevant.

In relation to FAR, published reports are more controversial. Meyer et al (15), in a single-center study in Germany, found an association between an extremely low NEC rate and a conservative EF regimen, meaning a slower FAR. Another single-center, case-control study including premature newborns found that volume increases over 20 mL kg^{-1} day^{-1} were significantly associated with NEC in more immature infants (13).

A meta-analysis of 10 randomized controlled trials from the Cochrane Collaboration database from 2017, concluded that evidence does not exist to show that advancing enteral feed volumes at daily increments of 15 to 20 mL/kg (compared with 30–40 mL/kg) reduces the risk of NEC or death in very preterm or VLBWI, including SGA infants (14). A recent large study of 2804 VLBWI showed no difference in NEC incidence when comparing 18 versus 30 mL kg^{-1} day^{-1} of FAR (22). We speculate that our finding of a significant difference regarding FAR only after adjusting for confounders might be because of selection of infants with intrinsic risk factors for the development of NEC. Hence, FAR might only represent a risk factor for a subgroup of VLBWI but not for all of them.

The optimal feeding strategy for the most immature infants remains unclear and lacks consensus. Standardized feeding regimens have been, however, associated with reduction of NEC risk (23,24). A recent systematic review of observational studies found an 80% reduction in relative risk of NEC with the use of standardized feeding protocols compared with nonstandardized regimens (RR: 0.22; 95% CI = 0.13–0.36; 15 studies, 18,160 infants) (23).

Different studies show that although the development of NEC is clearly associated with feeding, multiple other risk factors play a much more relevant role, in particular GA, BW, and male sex, similar to what was found in our study (1,2,5,6,8,25). SGA has been associated with increased risk for NEC in some studies (26,27). We found it was associated with increased risk of NEC/death. The need for mechanical ventilation was an important risk factor for both outcomes NEC and NEC/death. Assisted ventilation has also been reported to be associated with an increased risk of

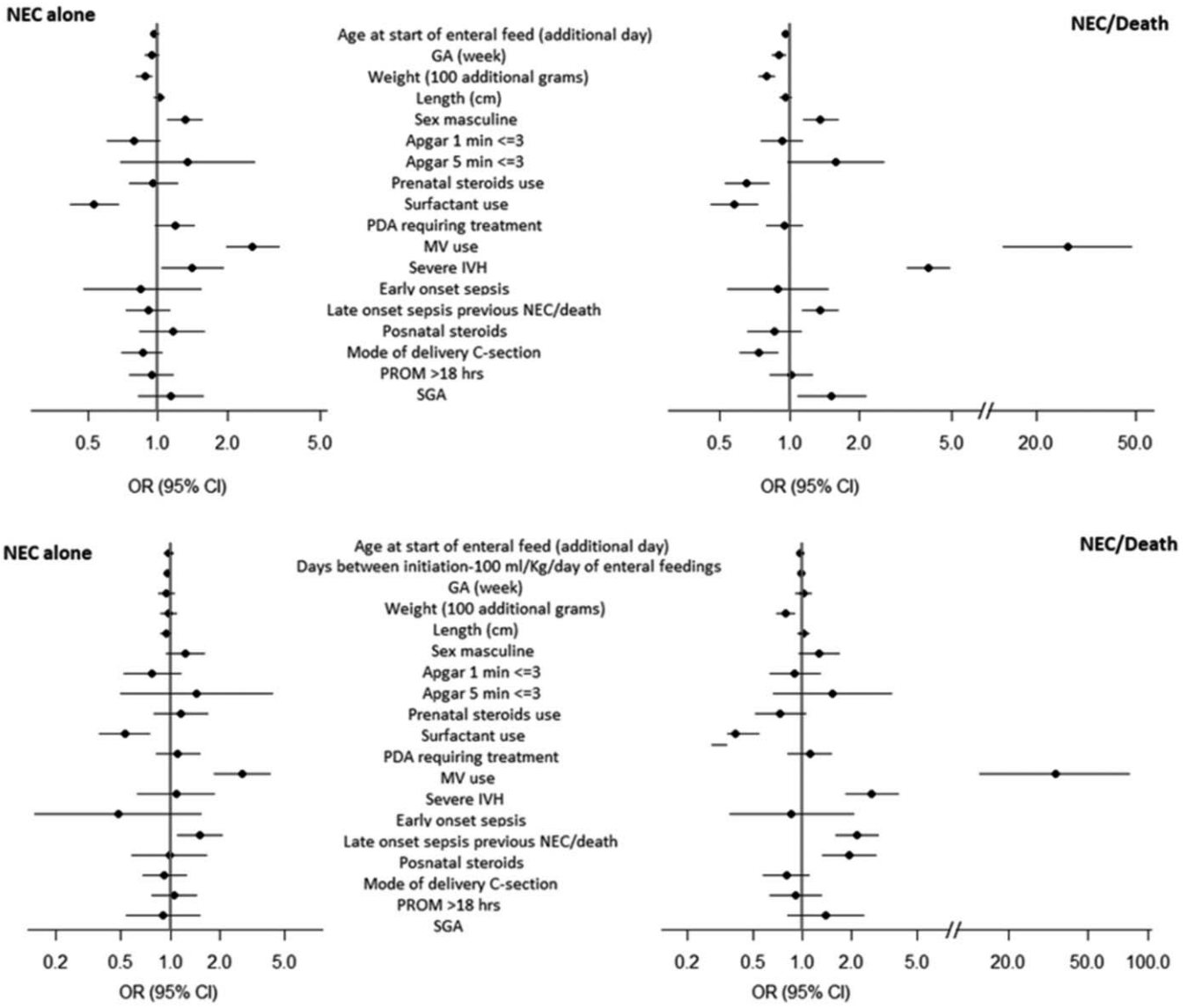

FIGURE 2. Assessment of the effect of initial enteral feeding on the type of outcome (necrotizing enterocolitis alone [left upper panel] or the composite outcome necrotizing enterocolitis/death [right upper panel]), all very-low-birth-weight infants were included. Assessment of the effect of FAR on the type of outcome (NEC alone [left lower panel] or the composite outcome NEC/death [right lower panel]), only infants who developed the outcome after reaching EF-100 were included. Adjusted OR and 95% CI are shown. 2001 to 2014, Neocosur neonatal network. 95% CI = 95% confidence interval; EF = enteral feeding; EF-100 = reaching 100 mL kg^{-1} day^{-1}; FAR = feeding advancement rate; GA = gestational age; IVH = intracranial hemorrhage; MV = mechanical ventilation; NEC = necrotizing enterocolitis; NEC/death = NEC with or without death; OR = odds ratio; PDA = patent ductus arteriosus; PROM = premature rupture of membranes; SGA = small-for-gestational age; VLBWI = very low birth weight infants.

NEC (28–31). It is unknown whether mechanical ventilation itself is a risk factor or that it might be reflecting more severely ill infants. Reports on surfactant therapy reveals contradictory findings for prediction of NEC (28,31). Our interpretation of the protective effect we found is that it decreases the use of mechanical ventilation when a strategy of early administration is used (32).

The finding that sIVH increases the risk for both NEC and NEC/death in our study population likely reflects that these are the sickest infants. The protective effect found with the use of antenatal steroids reemphasizes their multiple benefits in the VLBWI population. Conversely, we found that postnatal steroids were a risk factor for NEC. This agrees with other studies and is related with their known adverse effects in the immature intestinal gut with the fact that it is used in sicker infants (33). LOS was a risk factor for NEC, and the association of several pathogenic microorganisms with NEC has been described (34). PDA treatment has also been reported as a potential contributing factor for NEC but the evidence is inconclusive (25). In our study, it was associated with NEC/death, although after adjustment, this association was lost.

One of the limitations of this study is its retrospective nature, although the data were prospectively collected. Another limitation is that our database only includes ages at initial EF and at EF-100. Also, we only recently started differentiating whether feeding is with human milk or formula (since 2015). This is relevant as human

milk has been consistently shown to decrease the risk of NEC (11,25,35). In future studies, we will address the association between the use of human milk and several VLBWI outcomes. The strength of the study is the large population included, with VLBWI from multiple centers with different resources from 6 South American countries. The feeding regimen between Neocosur centers was not standardized, although most centers have standard protocols for their individual practices. This diversity among centers, along with the large included population, further enhances generalizability of findings.

CONCLUSIONS

In this large population-based study of VLBWI, early time of initial EF was not associated with NEC. A slower FAR was associated with lower risk of both outcomes. The studied feeding variables, some of which were statistically significant, are nonetheless of little clinical relevance and have less impact on the development of NEC or NEC/death compared with other variables. NEC's pathogenesis is complex, and finding the ''magic bullet'' to reduce its incidence seems rather unlikely. What may enlighten the road in the attempt to decrease the incidence of this devastating disease is an approach that combines a range of different strategies, including a standardized feeding protocol.

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