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Time to full enteral feeding for very low-birth-weight infants varies markedly among hospitals worldwide but may not be associated with incidence of necrotizing enterocolitis

The NEOMUNE-NeoNutriNet Cohort Study

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Original Communication

<AT>Time to Full Enteral Feeding for Very Low Birth Weight Infants Varies Markedly Among Hospitals Worldwide But May Not Be Associated With Incidence of Necrotizing Enterocolitis: The NEOMUNE-NeoNutriNet Cohort Study</AT>

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<AB>**Abstract**

Background: Transition to enteral feeding is difficult for very low birth weight (VLBW; ≤1500 g) infants, and optimal nutrition is important for clinical outcomes. *Method:* Data on feeding practices and short-term clinical outcomes (growth, necrotizing enterocolitis [NEC], mortality) in VLBW infants were collected from 13 neonatal intensive care units (NICUs) in 5 continents (n = 2947). Specifically, 5 NICUs in Guangdong province in China (GD), mainly using formula feeding and slow feeding advancement (n = 1366), were compared with the remaining NICUs (non-GD, n = 1581, Oceania, Europe, United States, Taiwan, Africa) using mainly human milk with faster advancement rates. *Results:* Across NICUs, large differences were observed for time to reach full enteral feeding (TFF; 8–33 days), weight gain (5.0–14.6 g/kg/d), Δz-scores (−0.54 to −1.64), incidence of NEC (1%–13%), and mortality (1%–18%). Adjusted for gestational age, GD units had longer TFF (26 vs 11 days), lower weight gain (8.7 vs 10.9 g/kg/d), and more days on antibiotics (17 vs 11 days; all $P <$ .001) than non-GD units, but NEC incidence and mortality were similar. *Conclusion:* Feeding practices for VLBW infants vary markedly around the world. The practice with much use of formula and long TFF in South China was associated with more use of antibiotics and slower weight gain, but apparently not with more NEC or higher mortality. Both infant- and hospital-related factors influence feeding practices for preterm infants. Multicenter, randomized controlled trials are required to identify the optimal feeding strategy during the first weeks of life. *(JPEN J Parenter Enteral Nutr. XXXX;xx:xx-xx)*</AB>

<KW>**Keywords**

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Clinical Relevancy Statement

Early transition to enteral nutrition, especially using mother's own milk, is believed to be important for growth, health, and development of preterm infants. Many factors may interact to determine the feeding practices at neonatal intensive care units (NICUs) around the world, including clinical traditions, available milk diets, and structural limitations at individual hospitals. Our cohort study shows that a relatively long time to reach full enteral feeding in 5 NICUs in South China with predominantly infant formula feeding was associated with more frequent use of antibiotics and less weight gain during the first 4 weeks of age, but apparently not with increased risk for necrotizing enterocolitis or death, relative to 8 other NICUs around the world, using faster feeding advancement rates with predominantly human milk. It may be important to vary nutrition strategies (eg, feeding advancement rate, criteria for withhold of feeding) according to different NICU settings (eg, availability of human milk).

Introduction

Preterm birth is a major cause of morbidity and mortality, especially for very low birth weight (VLBW; ≤1500 g) infants.[1] Survival of VLBW infants has increased in recent years because of novel perinatal interventions, but clear evidence for the optimal postnatal nutrition strategy is lacking. Optimal nutrition status may be critical to prevent adverse in-hospital outcome and support long-term development (eg, neurodevelopment).[2-5] Early and fast increase in enteral feeding is preferred, relative to prolonged use of parenteral nutrition (PN), to reduce sepsis, liver problems, and persistent gut immaturity.[6,7] Cochrane reviews show that early introduction and progressive advancement of enteral feeding are not associated with more necrotizing enterocolitis (NEC) than slow feeding,[8-11] but the evidence remains inconsistent.[12-14] Many feeding guidelines recommend early and progressive enteral feeding,[15,16] but it is challenging to adhere to such guidelines due to fear of NEC and nonspecific signs of feeding intolerance, especially for very immature infants[17] in hospitals with limited access to human milk.

There is a consensus that own mother's milk (MM) is the best diet during the first weeks after birth for high-risk preterm infants.[18,19] The evidence in favor of human donor milk (DM) is more variable,[20] whereas infant formula (IF) is inferior to MM with regard to clinical outcomes (eg, NEC, sepsis, mortality).[21] Therefore, in neonatal intensive care units (NICUs) with low availability of human milk, the clinical concern for NEC may be greater and the

time to reach full enteral feedings (TFF) longer. In addition, limited access to nutrition, medical, and surgical support in NICUs in low- and middle-income countries may influence the chosen nutrition practices.[22]

In this observational cohort study, we explored the nutrition practices and short-term clinical outcomes in 13 NICUs in 9 countries from 5 continents. Before this study, we informally observed that NICUs in the Guangdong province in South China (GD) had limited access to human milk and a slow feeding advancement, relative to other NICUs (non-GD) in our research network focusing on preterm nutrition. Thus, we specifically aimed to investigate whether the short-term clinical outcomes (growth, NEC incidence, mortality) differed between GD and non-GD NICUs. In addition, the GD region has a rapidly growing population and economy, with new hospital infrastructure, making it important to study how hospital-related factors may influence feeding practices and clinical outcomes. Data included time to full enteral feeding, diet type, duration of PN, and prebiotics and antibiotics use, together with growth, NEC, and mortality rates.

Methods

Study Design and Subjects

The NEOMUNE-NeoNutriNet was a combined retrospective and prospective cohort study to describe nutrition practices and short-term clinical outcomes in VLBW infants. Inclusion criteria were infants with a body weight ≤1500 g and admitted to the participating NICUs within 24 hours after birth. Exclusion criteria included major congenital abnormalities, metabolic disease, and transfer to another hospital within 24 hours of birth. Thirteen hospitals participated in the study across Europe (3), Oceania (2), North America (1), Africa (1), and Asia (6). Selection of the participating units was based on personal contact with the lead investigators and participation in the NEOMUNE research network (http://www.neomune.ku.dk).

Ethics

The study was approved by the ethical committee of VU University Medical Center, Amsterdam, the Netherlands, and at individual hospitals when required. Parental informed consents were obtained in 1 hospital but were not necessary in others because collected data were anonymous and were routinely collected as part of clinical care. A contract research organization was responsible for regulatory and safety aspects of the database (Academic

Medical Center, Amsterdam, the Netherlands).

Data Collection and Outcomes

Entry into the web-based database started on September 15, 2013. For each unit the aim was to include at least 100 infants, born consecutively between January 1, 2011, and September 15, 2014. Case report forms were used to collect information from medical and nursing records including infant demographics (gestational age [GA] and anthropometrics at birth, gender, delivery mode, antenatal corticosteroids), nutrition regimens (timing and type of enteral nutrition [EN] and PN, time to reach enteral feeding volumes of 120 [TFF120] or 150 mL/kg/d [TFF150]), use of probiotics, and clinical outcomes (use of antibiotics, respiratory support, NEC incidence, defined as Bell stage ≥II[23]), all-cause mortality, and weekly anthropometric data (eg, weight, length, head circumference). Small for gestational age (SGA) was defined as <10th percentile for weight at birth. The Newcastle unit did not record TFF120, and the Taiwan site did not collect data on infants who died. All data were collected until postconceptional age (PCA) 37 weeks, or less if infants were transferred to a step-down unit, discharged to home, discharged on parental request before reaching discharge criteria, or died. Complying with the recommendations on reporting growth-related outcomes in preterm infants,[24] the growth was reported from birth with the Fenton 2013 growth chart[25] as the growth reference. Weight was reported in z-scores, and Δz-scores from birth to 28 days were used to assess changes in weight over time. The exponential method by Patel et al[26] was used to calculate weight gain velocity.

Statistical Analysis

All statistical analyses were performed using the R software package (version 3.2.2). Data were summarized using means and SDs, medians and interquartile ranges (IQRs), numbers and percentages, as appropriate. Median and IQR were used in cases of right-censored time-to-event data (eg, TFF). Comparisons of demographic characteristics listed in Table 1 between GD and non-GD NICUs were based on analysis of variance for continuous outcomes (eg, body weight [BW]) and logistic regression models for binary outcomes (eg, SGA). In Table 2, all outcome comparisons between GD and non-GD units were performed with or without adjustments for GA. Time-to-event data were compared using Cox proportional hazard models, and other continuous outcomes (eg, weight) were compared based on analysis of variance. Binary outcomes (eg, mortality) were compared using logistic

regression models. Adjustment for GA was done using the groups <28, 28, 29, 30, 31, 32, and >32 weeks because of the nonlinear relation between GA and clinical outcomes. Nonparametric Kruskal-Wallis test was used when normal distribution could not be achieved. A P-value <.001 was considered significant, whereas .01 < P < .001 as a tendency to an effect. We used this very restrictive approach to statistical differences, considering the large number of comparisons performed, and the possible inflation of significancy by cluster effects.

Results

A total of 2947 infants (GD, n = 1366; non-GD, n = 1581) were collected from the 13 NICUs that each included >100 consecutively born VLBW infants (except 1 unit with n = 93; Table 1). Mean GA and BW ranged widely among NICUs and specifically, infants in the 5 GD units had higher GA and BWs (30.3 ± 2.1 weeks, 1250 ± 182 g) than the infants from non-GD units (29.0 ± 2.6 weeks, 1086 ± 262 g, both P < .001; Table 1). Likewise, birth length and head circumference were higher in GD infants (both P < .001; Table 1). z-Scores of BW, birth length, and head circumference did not differ (Table 1). The overall mean values for proportion of SGA infants (~20%), singletons (~70%), and caesarean deliveries (~60%) were similar between GD and non-GD units (Table 1), whereas the proportion of males was higher in the GD units (56% vs 48% in non-GD units; P < .001). Use of antenatal steroids was less prevalent in GD vs non-GD units (49% vs 83%), and likewise there was less use of probiotics (21% vs 35%; all P < .001; Table 1).

As predicted before the study, most infants in the 5 GD units were formula-fed during the first 4weeks (Figure 1). The proportion of infants receiving exclusively IF during the first 4 weeks was 74% in GD vs 5% in non-GD units (P < .001). Provision of MM varied widely among NICUs, and DM was available in only 3 units (Amsterdam, Copenhagen, and Perth). Nine units used human milk fortifier for some infants (14% in GD and 67% in non-GD units), being initiated from 10 to 24 days after birth (Table 1). The GD units reported more early discharge on parental request, relative to non-GD units (22% vs 1%; P < .001).

Among the clinical outcomes (Table 2), mortality (1%–18% across all NICUs) was similar between GD and non-GD units (5% vs 7%), with or without adjustment for GA. The frequency and duration of intubated ventilation were less in GD units (43% vs 51% and 2 vs 6 days, respectively; both P < .001), but the significances disappeared after GA adjustment. The median age for introduction of enteral feeding was older in GD vs non-GD units (3 vs 2

days; $P < .001$), both with and without GA adjustment. TFF120 and TFF150 were 26 and 34 days, respectively, compared with 11 and 15 days for the non-GD units (both $P < .001$; Table 2). Figure 2 shows TFF120 in relation to postnatal days for all units, and the median TFF120 and TFF150 were 8–33 and 11–47 days, respectively (Table 2). In Figure 3, TFF120 for the individual units are depicted together with 4 key clinical outcomes adjusted for the differences in GA among infants (mortality, growth rate, NEC incidence, antibiotics use). PN was administered for a longer time in GD vs non-GD units, with or without GA adjustment (25 vs 13 days; $P < .001$; Table 2). Growth velocity for weight was 5.0–14.6 g/kg/d (0–28 days) and Δz-scores −0.54 to −1.64, and both variables were lower in GD vs non-GD hospitals (8.7 vs 10.9 g/kg/d and −1.23 vs −0.91, respectively), with or without GA adjustment (Table 2). Growth velocity and z-score change for length did not differ between GD and non-GD units. The z-score for head circumference decreased less in GD vs non-GD units, but the difference disappeared after GA adjustment (Table 2).

Antibiotics were used more in GD units compared with non-GD units (99% vs 92% and 17 vs 11 days; both $P < .001$; Table 2). The incidence of NEC varied widely among hospitals (1%–13%; Table 2), with the mean day and PCA at onset being 8–27 days and 28.4–33.6 weeks, respectively. NEC rates tended to be lower in GD vs non-GD hospitals (4% vs 6%; $P = .009$), with fewer severe NEC cases (Bell score II/III, 39/9 vs 47/33; $P = .007$), earlier age at onset (13 vs 21 days; $P < .001$), and fewer NEC surgeries (16% vs 42%; $P = .001$). However, these differences became insignificant when adjusted for GA (P_2-values in Table 2). The first stool was passed earlier in GD units with or without adjustment for GA (2 vs 3 days in non-GD units; $P < .001$).

There was considerable heterogeneity in demographic and outcome data among the 8 non-GD units that practiced early and fast progression of human milk feeding (Figure 1, Tables 1 and 2). Particularly, Ibadan (n = 150, Africa) tended to differ from the others (n = 1431 from mainly Western countries) with a higher mortality rate (18% vs 6 %), GA (30.5 vs 28.8 weeks), and BW (1223 vs 1072 g); more SGA infants (27% vs 18%); and fewer singletons (55% vs 71%), caesarean deliveries (44% vs 64%), antenatal steroid treatments (31% vs 89%), infants provided intubated respiratory support (4% vs 56%), and parenteral amino acids (51% vs 94%; all $P < .01$; Tables 1 and 2).

Discussion

Our study demonstrates marked differences in nutrition practices and short-term clinical

outcomes for hospitalized VLBW infants around the world. Specifically, the predominant use of formula, and a long TFF for the 5 NICUs in South China, was associated with more use of antibiotics and less weight gain during the first 4 weeks of life, but this apparently did not affect the in-hospital NEC or mortality rates, compared with the remaining units. Although the TFF depends on the infant's clinical conditions, the significant variability among NICUs demonstrates that many other factors contribute to the chosen nutrition practice. These include availability of human milk and PN, physical infrastructure of NICUs, clinical and cultural traditions, and the perception of doctors and nurses toward signs of feeding intolerance and NEC. Thus, a combination of infant- and hospital-related factors determines the time to full enteral feeding in NICUs (Figure 4). It remains important to investigate whether these differences for in-hospital feeding regimens and short-term clinical outcomes have long-term effects on infant health and development.

The more conservative approach to volume advancement in South China resulted in a TFF that was more than twice of that in other hospitals. Although longer PN was used to compensate for slow enteral feeding advancement, a reduced weight gain was observed in GD units, reflecting the difficulties in achieving adequate growth during the first 4 weeks using mainly PN. Importantly, this was associated with 50% more days receiving antibiotics, probably because of an increased risk for infections from indwelling catheters for PN or differences in clinical guidelines. Differences in use of antenatal steroids and respiratory support might also have influenced both TFF and NEC rates. Unknown confounders, such as hospital-specific gut colonization, genetics, differences in diagnostic criteria (Bell scoring), and access to surgery for NEC may also contribute to differences among units. Further, we did not know the NEC incidence for infants discharged early to step-down units or to home after parental request. Consequently, the differences in NEC incidences must be interpreted with caution.

Formula feeding has been associated with a higher risk for feeding interruption because of emesis, abdominal distension, bloody stools, or suspicion of NEC,[27] and increased NEC rates.[28] Consequently, predominant use of formula feeding may have contributed to the more conservative enteral feeding in the GD units. Moreover, clinical features of feeding intolerance, used as early signs of NEC, are nonspecific and vary widely among units and clinicians. This may lead to unjustified delay in enteral feeding, regardless of diet.[29] More research is required to evaluate and predict the clinical consequences of the variable symptoms of feeding intolerance. Nevertheless, it may be important to alter feeding

advancement rate and criteria for withholding feeding according to the availability of human milk. However, our data cannot be used to provide direct evidence to support specific diet and feeding regimens, because this would require large randomized clinical trials (RCTs). The advantages of MM for preterm infants are well-known, leading health authorities around the world to strongly recommend the use of MM for VLBW infants.[16,30] Unfortunately, not all mothers can provide their infants with sufficient amounts of MM, especially when initiation of lactation is delayed after preterm birth.[31,32] It is difficult to increase the availability of human milk if the hospital infrastructure does not allow cohospitalization of mothers, lactation support, or DM banking. The African NICU (Ibadan) had a relatively high mortality rate, despite early feeding with MM, which may be related to sepsis[22] and more limited use of some clinical treatments (eg, respiratory and PN support). The presence of human milk banks may positively influence breast-feeding rates for preterm infants, and several feeding guidelines propose to use DM when MM is not available or insufficient.[33,34] The number of countries with DM banks has increased,[35,36] and in the 3 non-GD units with access to DM, TFF120 was reached already after 8–11 days. At 2 of these units, enteral feeding started on the first day after birth, compared with days 2–4 in units without access to DM. Delaying feeding introduction until MM becomes available is common (rather than starting on IF), especially for the smallest infants, but limited scientific evidence is available.[14,17] Delayed start of enteral feeding often reflects a concern for NEC, but there is also a risk that enteral fasting after birth will delay intestinal maturation, induce mucosal atrophy, and reduce the digestive capacity.[4] In a recent randomized trial, there was no difference in NEC and sepsis rates between preterm infants who received DM or IF as supplement to MM for the first 10 days after birth.[20] Intestinal maturation may not be optimal unless the mother's own colostrum is given as the first feed.[37] Interestingly, bovine colostrum, given as a supplement to MM during the first 14 days, reduced TFF in 2 GD units in a recent pilot trial.[38]

Our study has several strengths and limitations. A major strength is the wide geographic variation in the participating NICUs with a large number of infants, which enabled a comparison of nutrition practices across several continents. Limitations include that the design was primarily retrospective, with some missing data and potentially important unmeasured confounders. Clinical outcomes (eg, NEC, mortality) were unclear for infants subjected to early discharge on parental request in GD units and discharged to step-down units in European units. In some GD units, parents asked for early discharge if their infant

was stable before reaching the required body weight for discharge (ie, 2000 g). Other reasons for discharge on parental request may include economic or social limitations, leading to giving up further treatments or transferring to another hospital near home. Finally, it is important to note that participating NICUs in this study may not be representative of those in their respective countries or continents, and clinical routines may be changing rapidly in newly urbanized regions, like South China. Different hospital settings and infant demographics and genetics may have a different balance of risks and benefits for selected treatments. Thus, trials performed in 1 hospital or region cannot always be translated to other settings.

In summary, nutrition practices and clinical outcomes varied markedly among NICUs worldwide. Much longer time to full enteral feeding, more use of formula feeding and antibiotics, prolonged use of PN, and lower weight gain were observed in NICUs in the GD region in South China, but this did not appear to be associated with increased risk for in-hospital NEC or death. It may be important to vary nutrition strategies (eg, advancement rate, criteria for withholding feeding) according to different NICU settings (eg, availability of human milk and PN, access to surgery for NEC). Large RCTs are required to identify the optimal nutrition strategies for VLBW preterm infants, and our data provide valuable information for planning such trials. The results have contributed to the design of an ongoing large randomized trial comparing supplemental bovine colostrum with IF during the first 14 days on TFF in some GD hospitals (ClinicalTrials.gov identifier: NCT03085277). It is also relevant, based on the present observational results, to investigate in RCTs how slow vs fast feeding advancement rate, different feeding intolerance assessments, and time and duration of antibiotics use may affect clinical outcomes, especially in hospitals with limited access to human milk. However, clinical routines for VLBW infants are changing rapidly (eg, use of human milk and antibiotics), both in China and in many other areas of the world. Thus, it may soon become relevant in follow-up observational studies to compare the present data from the NEOMUNE-NeoNutriNet database with updated data on clinical routines and outcomes for VLBW infants.

with the data collection.

Statement of Authorship

J. B. van Goudoever, G. Greisen, and P. T. Sangild contributed to the conception of the research. M. de Waard, Y. Li, J. B. van Goudoever, G. Greisen, and P. T. Sangild contributed to the design of the research; M. de Waard, Y. Li, Y. Zhu, A. I. Ayede, J. Berrington, F. H. Bloomfield, O. O. Busari, B. E. Cormack, N. D. Embleton, G. Greisen, Z. He, Y. Huang, X. Li, H.-C. Lin, J. Mei, P. P. Meier, C. Nie, A. L. Patel, T. Skeath, K. Simmer, O. O. Tongo, S. Uhlenfeldt, S. Ye, X. Ye, C. Zhang, and P. Zhou contributed to the acquisition of the data; Y. Li, G. Greisen, and C. Ritz contributed to the analysis of the data; M. de Waard, Y. Li, F. H. Bloomfield, N. D. Embleton, J. B. van Goudoever, G. Greisen, P. T. Sangild, and K. Simmer contributed to the interpretation of the data. M. de Waard, Y. Li, and P. T. Sangild drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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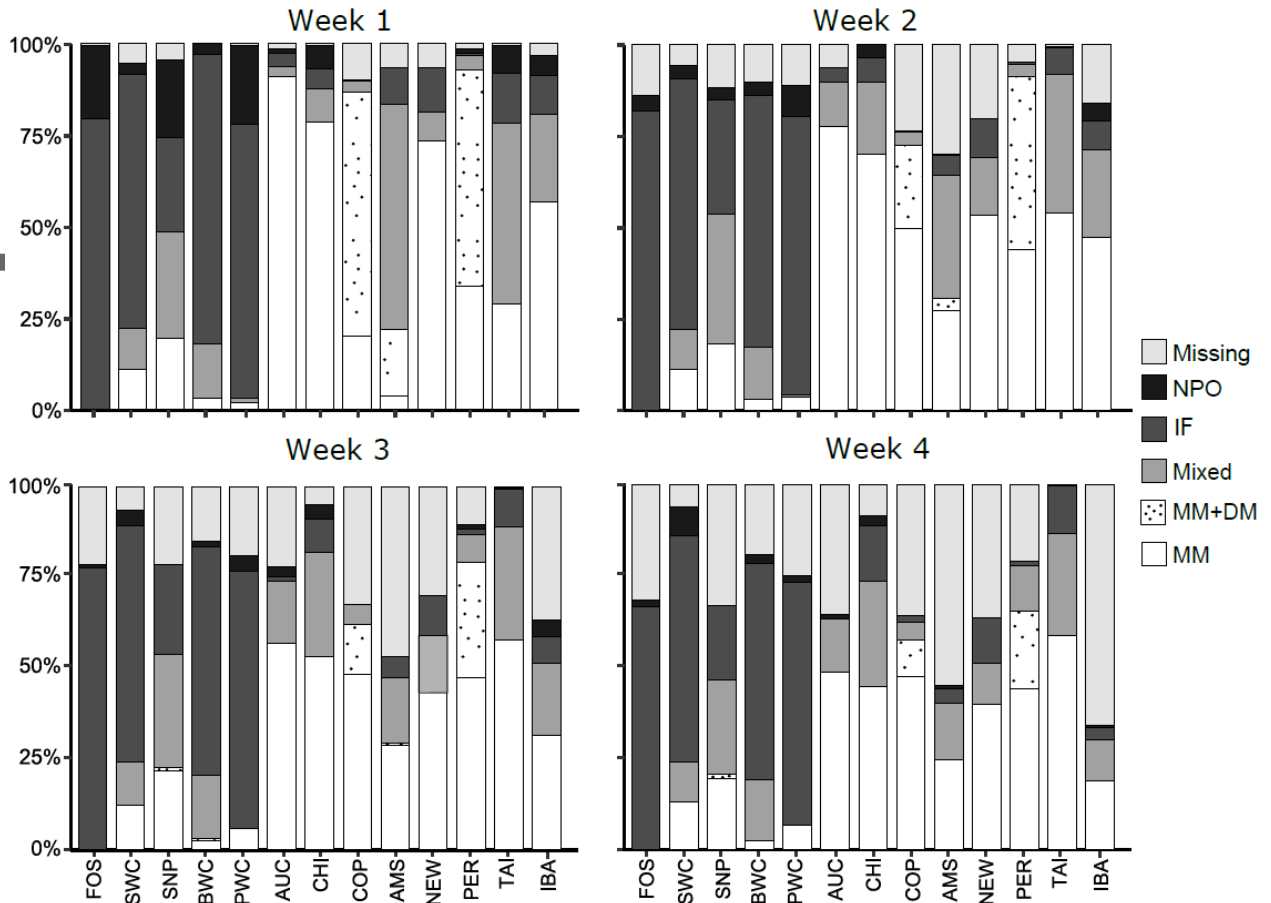
Figure 1. Type of enteral nutrition 0–28 days after birth in 13 neonatal intensive care units (NICUs) around the world. AMS, Academic Medical Center; AUC, University of Auckland and Newborn Service, National Women's Health; BWC, Shenzhen Bao'an Maternal and Child Health Hospital; CHI, Rush University Children's Hospital; COP, University of Copenhagen; FOS, Foshan Woman and Children's Hospital; IBA, University of Ibadan and University College Hospital; IF, exclusive infant formula; MM, exclusively own mother's milk; MM+DM, own mother's milk and/or donor milk; mixed, MM+DM and IF; missing, missing values due to lack of data, infant death, or discharge; NEW, Newcastle Hospitals NHS Foundation Trust; NPO, nil per os; PER, University of Western Australia and King Edward Memorial Hospital; PWC, Guangdong Provincial Women & Children's Hospital; SNP, Shenzhen Nanshan People's Hospital; SWC, Shenzhen Maternity & Child Health Care Hospital; TAI, Children's Hospital of China Medical University.
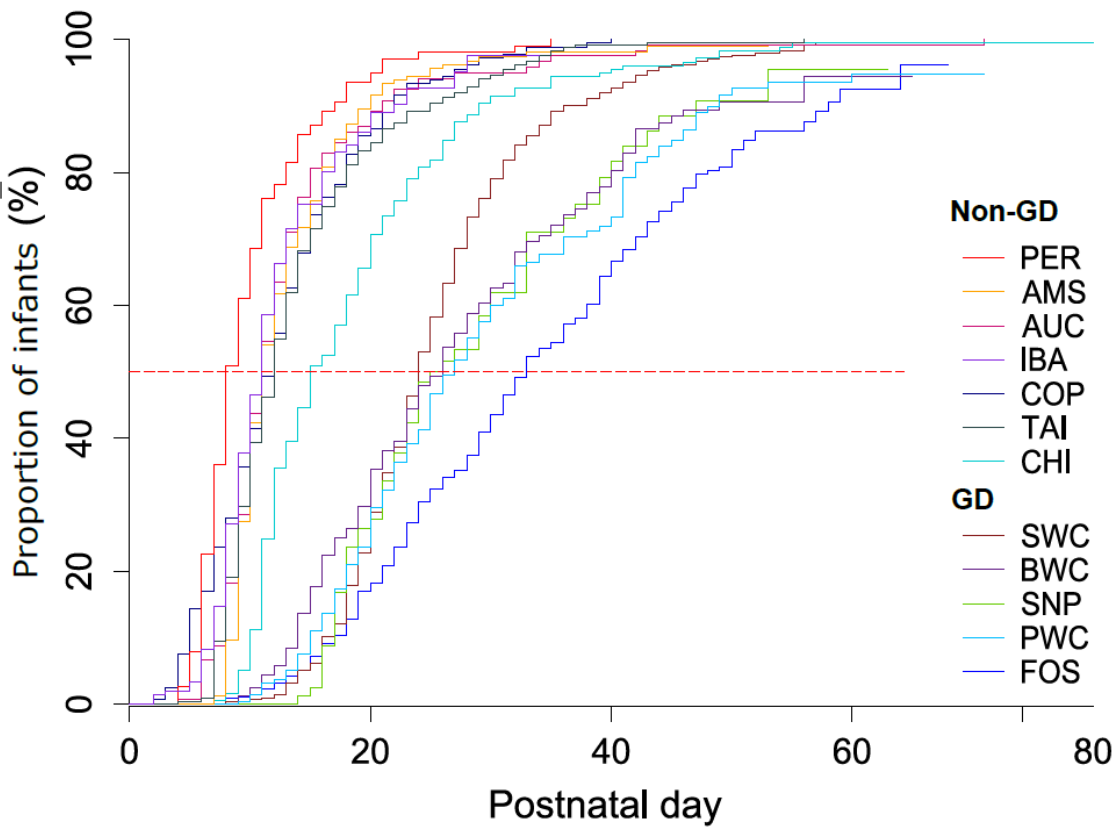
Figure 2. Proportion of infants reaching enteral feeding volumes of 120 mL/kg/d relative to infant age in South China units (GD) and other units (non-GD) around the world. AMS, Academic Medical Center; AUC, University of Auckland and Newborn Service, National Women's Health; BWC, Shenzhen Bao'an Maternal and Child Health Hospital; CHI, Rush University Children's Hospital; COP, University of Copenhagen; FOS, Foshan Woman and Children's Hospital; GD, Guangdong province in China; IBA, University of Ibadan and University College Hospital; PER, University of Western Australia and King Edward Memorial Hospital; PWC, Guangdong Provincial Women & Children's Hospital; SNP, Shenzhen Nanshan People's Hospital; SWC, Shenzhen Maternity & Child Health Care Hospital; TAI, Children's Hospital of China Medical University.
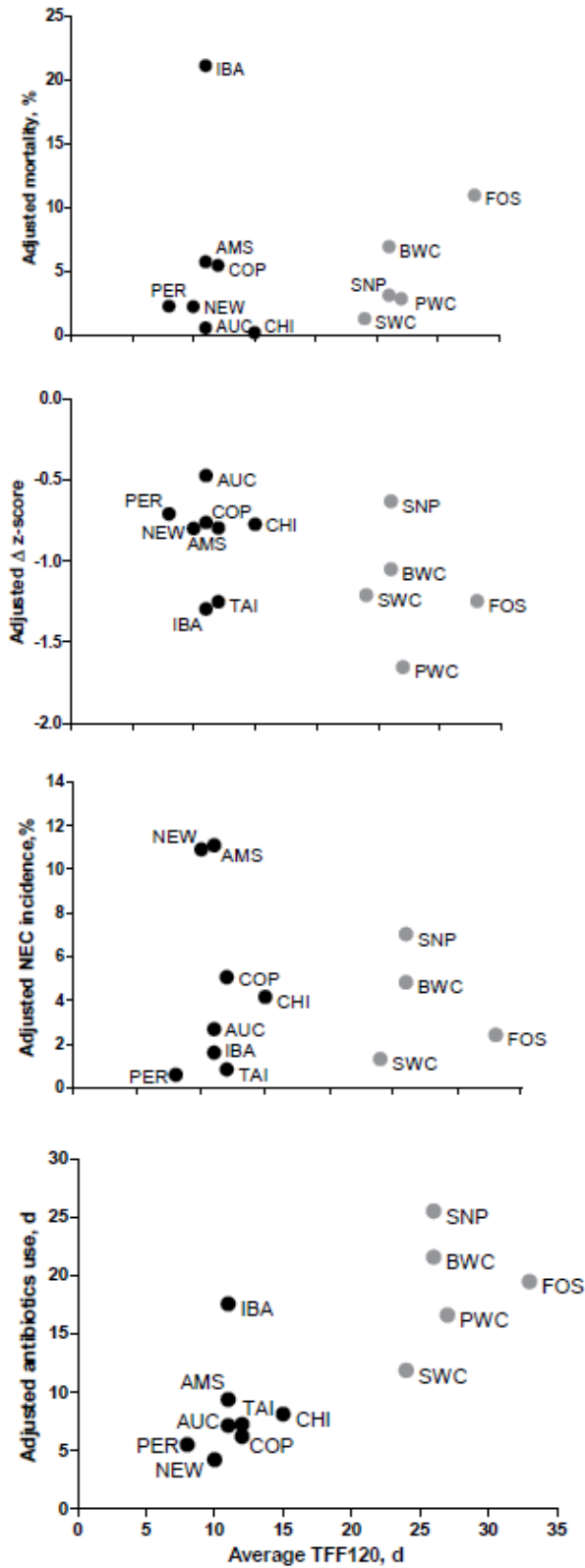
Figure 3. Association between time to full feeding (median days to 120 mL/kg/d) and gestation age–corrected mortality (A), weight Δz-scores at 0–28 days (B), necrotizing enterocolitis incidence (C), and days receiving antibiotics (D) in South China (Guangdong)

hospitals (gray symbols) and other hospitals around the world (black symbols). AMS, Academic Medical Center; AUC, University of Auckland and Newborn Service, National Women's Health; BWC, Shenzhen Bao'an Maternal and Child Health Hospital; CHI, Rush University Children's Hospital; COP, University of Copenhagen; FOS, Foshan Woman and Children's Hospital; IBA, University of Ibadan and University College Hospital; NEW, Newcastle Hospitals NHS Foundation Trust; PER, University of Western Australia and King Edward Memorial Hospital; PWC, Guangdong Provincial Women & Children's Hospital; SNP, Shenzhen Nanshan People's Hospital; SWC, Shenzhen Maternity & Child Health Care Hospital; TAI, Children's Hospital of China Medical University; TFF120, time to reach enteral feeding volumes of 120 mL/kg/day.
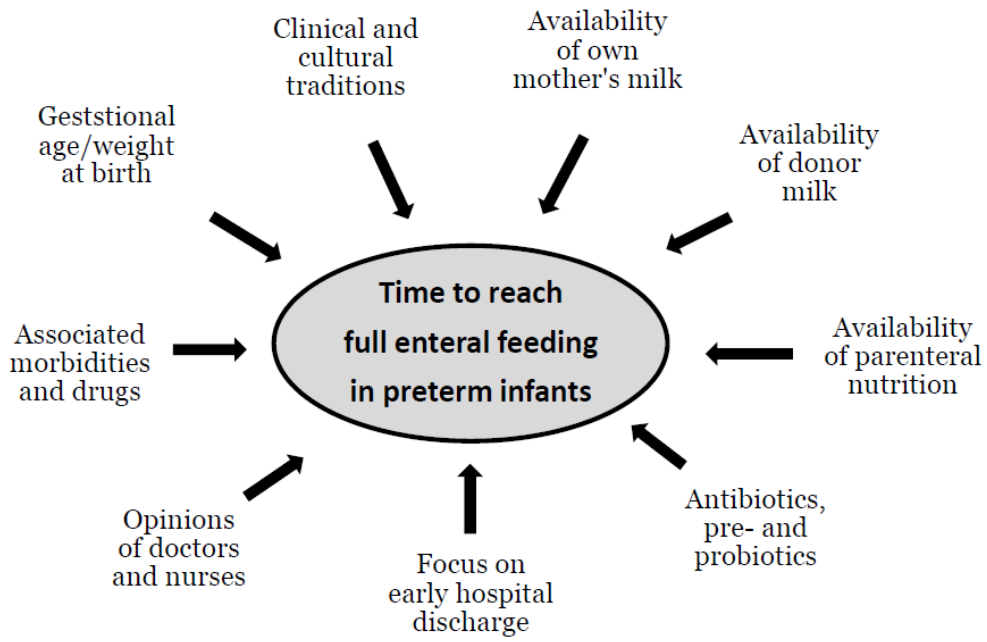
Figure 4. Many different factors influence the time taken to reach full enteral feeding in preterm infants. These factors are related to the infants, but also to the parents, clinical staff, and hospital conditions.

Table 1. Demographic Characteristics at Birth and Use of Antenatal Steroids, Milk Fortification, and Probiotics in South China NICUs (GD) and in Other Units Around the World (Non-GD).

Hospital	FOS	SWC	SNP	BWC	PWC	AUC	CHI	COP	AMS	NEW	PER	TAI	IBA	GD	Non-GD
Total included	407	458	93	167	241	160	177	284	270	139	152	249	150	1366	1581
Gestational age, weeks	30.4 (2.1)	30.3 (2.2)	30.4 (2.0)	29.7 (2.0)	30.5 (2.1)	29.0 (2.7)	28.3 (2.5)	28.0 (2.5)	28.6 (2.2)	28.4 (2.8)	29.4 (2.5)	29.9 (2.6)	30.5 (2.4)	30.3 (2.1)	29.0 (2.6)[a]
Birth weight g	1237 (184)	1254 (177)	1245 (219)	1250 (183)	1262 (172)	1101 (262)	1025 (252)	990 (267)	1070 (258)	1043 (280)	1127 (257)	1165 (236)	1223 (191)	1250 (182)	1086 (262)[a]
z-Score	−0.56 (0.99)	−0.44 (1.06)	−0.66 (0.90)	−0.20 (0.84)	−0.55 (1.05)	−0.32 (1.03)	−0.25 (0.94)	−0.31 (0.93)	−0.24 (0.95)	−0.34 (0.92)	−0.45 (0.9)	−0.56 (1.05)	−0.62 (1.24)	−0.48 (1.01)	−0.38 (1.00)
Birth length cm	38 (4)	39 (4)	38 (3)	39 (3)	38 (3)	37 (4)	36 (3)	36 (4)	36 (3)	UNK	37 (4)	38 (3)	38 (3)	39 (3)	37 (4)[a]
z-Score	−0.43 (1.48)	−0.02 (1.59)	−0.64 (1.18)	0.06 (1.04)	−0.57 (1.45)	−0.12 (1.24)	−0.31 (1.08)	−0.2 (1.12)	−0.43 (1.18)	UNK	−0.23 (1.14)	−0.32 (1.30)	−0.51 (1.30)	−0.27 (1.47)	−0.30 (1.20)
Birth head circumference cm	26.7 (1.9)	27.1 (2.2)	27.3 (1.8)	27.0 (1.7)	27.3 (1.8)	26.3 (2.1)	25.1 (2.1)	25.3 (2.7)	25.9 (2.4)	25.6 (1.9)	26.2 (2.4)	26.3 (2.1)	27.3 (1.8)	27.0 (2.0)	26.0 (2.3)[a]
z-Score	−0.6	−0.27	−0.33	−0.02	−0.27	0.05	−0.33	−0.11	−0.02	−0.14	−0.29	−0.50	−0.21	−0.36	−0.20

	3 (1.41)	(1.62)	(1.16)	(1.08)	(1.36)	(1.06)	(1.11)	(0.98)	(1.08)	(1.06)	(1.12)	(1.23)	(1.34)	(1.44)	(1.14)
Small for gestational age, n (%)	84 (21)	86 (19)	24 (26)	19 (11)	52 (22)	27 (17)	28 (16)	49 (17)	40 (15)	24 (17)	28 (18)	61 (24)	40 (27)	265 (19)	297 (19)
Male, n (%)	230 (57)	231 (51)	43 (46)	108 (65)	153 (63)	80 (50)	95 (54)	130 (46)	135 (50)	71 (51)	72 (47)	116 (47)	66 (44)	765 (56)	765 (48)[a]
Singleton, n (%)	278 (69)	270 (59)	72 (78)	124 (74)	164 (68)	115 (72)	151 (85)	165 (58)	204 (76)	29 (73)	116 (76)	170 (68)	82 (55)	908 (67)	1032 (70)
Caesarean section, n (%)	251 (62)	312 (68)	62 (67)	65 (39)	142 (59)	104 (65)	117 (66)	193 (68)	154 (57)	71 (52)	99 (65)	178 (71)	66 (44)	832 (61)	982 (62)
Steroids															
Any steroids, n (%)	155 (38)	106 (70)	74 (80)	85 (52)	92 (38)	157 (98)	164 (93)	203 (88)	235 (87)	131 (94)	141 (93)	193 (78)	47 (31)	512 (49)	1271 (83)[a]
Complete steroids, n (%)	82 (20)	75 (50)	52 (57)	37 (22)	65 (27)	119 (74)	124 (70)	170 (73)	154 (57)	97 (70)	118 (78)	155 (62)	28 (19)	311 (30)	965 (63)[a]
Human milk fortifier															
n (%)	0 (0)	167 (37)	22 (24)	0 (0)	8 (3)	138 (86)	135 (76)	163 (57)	187 (69)	UNK [b]	140 (92)	197 (79)	0 (0)	197 (14)	960 (67)[a]
Day of life	—	24 (8)	23 (8)	—	22 (8)	10 (7)	20 (9)	21 (9)	12 (5)	UNK [b]	11 (5)	15 (9)	—	24 (8)	15 (8)[a]
Probiotics, n (%)	67 (17)	38 (11)	0 (0)	79 (47)	78 (33)	106 (67)	0 (0)	227 (81)	0 (0)	34 (81)	109 (72)	43 (17)	0 (0)	262 (21)	515 (35)[a]
Observation	35	40	32	42	37	38	58	46	30	45	46	49	23	38	42

period,[c] days	(18)	(17)	(16)	(18)	(18)	(26)	(20)	(27)	(23)	(28)	(22)	(18)	(12)	(18)	(25)[a]

Data are presented as mean (SD) unless otherwise stated.

AMS, Academic Medical Center; AUC, University of Auckland and Newborn Service, National Women's Health; BWC, Shenzhen Bao'an Maternal and Child Health Hospital; CHI, Rush University Children's Hospital; COP, University of Copenhagen; FOS, Foshan Woman and Children's Hospital; GD, Guangdong province in China; IBA, University of Ibadan and University College Hospital; NEW, Newcastle Hospitals NHS Foundation Trust; PER, University of Western Australia and King Edward Memorial Hospital; PWC, Guangdong Provincial Women & Children's Hospital; SNP, Shenzhen Nanshan People's Hospital; SWC, Shenzhen Maternity & Child Health Care Hospital; TAI, Children's Hospital of China Medical University; UNK, unknown.

[a]Significant difference between CN and non-CN ($P < .001$).

[b]Human milk fortifier was used, but exact data are missing.

[c]Data were collected from <24 hours after birth to postconceptional age 37 weeks, or less if infants were transferred to a different (step-down) unit, discharged to home (including discharge on parental request), or died.

Table 2. Anthropometric and Clinical Outcomes in South China (GD) NICUs and Other NICUs Around the World (Non-GD).

Hospital	FOS	SWC	SNP	BWC	PWC	AUC	CHI	COP	AMS	NEW	PER	TAI	IBA	GD	Non-GD	P_1	P_2
Mortality (%)	42 (10)	7 (2)	3 (3)	14 (8)	7 (3)	2 (1)	1 (1)	38 (13)	29 (11)	7 (5)	6 (4)	UNK	27 (18)	73 (5)	110 (7)	NS	NS
Intubation ventilation																	
n (%)	182 (46)	131 (30)	26 (28)	98 (59)	145 (60)	84 (53)	141 (80)	144 (51)	170 (63)	90 (65)	85 (56)	78 (32)	6 (4)	582 (43)	798 (51)[a]	—[a]	NS
Days[b]	3 (7)	1 (3)	2 (3)	4 (6)	3 (5)	5 (10)	11 (16)	5 (11)	8 (14)	8 (13)	3 (9)	4 (11)	0 (0)	2 (5)	6 (12)[a]	—[a]	NS
Start enteral nutrition																	
n (%)	371 (92)	441 (97)	83 (89)	165 (99)	227 (94)	156 (99)	177 (100)	282 (99)	268 (100)	137 (99)	149 (99)	249 (100)	144 (96)	1287 (95)	1562 (99)	—[a]	—[a]
DOL, median (IQR)	4 (2–6)	2 (2–3)	3 (3–6)	2 (2–3)	3 (1–6)	2 (1–2)	3 (3–5)	1 (1–2)	1 (1–1)	4 (2–5)	2 (2–3)	2 (2–4)	3 (3–5)	3 (2–5)	2 (1–3)	—[a]	—[a]
TFF (120 mL/kg/d)																	
n (%)	233 (58)	392 (86)	58 (62)	126 (75)	160 (66)	141 (88)	176 (99)	235 (83)	204 (76)	UNK	146 (96)	245 (98)	119 (79)	969 (71)	1266 (88)	—[a]	—[a]
DOL, median (IQR)	33 (23–45)	24 (20–29)	26 (19–37)	26 (17–38)	27 (20–41)	11 (9–14)	15 (12–22)	12 (8–16)	11 (9–15)	UNK	8 (7–11)	12 (9–17)	11 (8–14)	26 (20–37)	11 (9–16)	—[a]	—[a]
TFF (150 mL/kg/d)																	
n (%)	155 (38)	373 (82)	41 (44)	90 (54)	124 (51)	138 (86)	171 (97)	222 (78)	173 (64)	117 (85)	144 (95)	166 (67)	110 (73)	783 (58)	1241 (79)	—[a]	—[a]

DOL, median (IQR)	47 (30–60)	30 (24–36)	38 (25–49)	37 (26–61)	37 (28–50)	12 (10–16)	19 (14–28)	14 (10–20)	15 (12–22)	13 (10–17)	11 (8–16)	35 (20–68)	13 (11–18)	34 (26–49)	15 (11–25)	—[a]	—[a]
Parenteral amino acids																	
n (%)	389 (96)	455 (100)	92 (99)	167 (100)	233 (97)	154 (96)	176 (99)	231 (81)	269 (100)	131 (94)	148 (97)	236 (95)	76 (51)	1336 (98)	1421 (90)	—[a]	—[a]
Days[b]	27 (15)	24 (10)	25 (12)	28 (13)	24 (15)	15 (11)	22 (15)	11 (9)	15 (11)	14 (14)	11 (7)	11 (7)	3 (5)	25 (13)	13 (11)	—[a]	—[a]
Parenteral lipids																	
n (%)	293 (72)	453 (99)	90 (97)	159 (95)	185 (77)	151 (94)	176 (99)	221 (78)	269 (100)	131 (94)	145 (95)	80 (32)	0 (0)	1180 (86)	1173 (74)	—[a]	—[a]
Days[b]	18 (16)	20 (10)	24 (12)	21 (12)	16 (14)	13 (11)	22 (15)	9 (8)	14 (11)	14 (14)	9 (7)	4 (7)	0	19 (13)	11 (12)	—[a]	—[a]
Weight GV																	
g/kg/d[c]	8.7 (4.1)	9.3 (2.3)	12.7 (3.1)	10.5 (3.4)	5.0 (3.5)	14.6 (4.1)	12.1 (3.8)	11.2 (3.8)	11.0 (4.6)	10.0 (4.4)	12.6 (4.0)	8.0 (4.3)	8.8 (5.7)	8.7 (4.2)	10.9 (4.6)	—[a]	—[a]
Δz-Score[d]	−1.24 (0.48)	−1.18 (0.31)	−0.62 (0.38)	−1.04 (0.41)	−1.64 (0.42)	−0.54 (0.49)	−0.83 (0.51)	−0.86 (0.48)	−0.83 (0.50)	−0.88 (0.45)	−0.73 (0.41)	−1.25 (0.42)	−1.30 (0.67)	−1.23 (0.50)	−0.91 (0.53)	—[a]	—[a]
Length GV																	
cm/week[c]	0.8 (0.6)	1.0 (0.6)	0.9 (0.6)	0.9 (0.4)	UNK	1.0 (0.5)	0.8 (0.5)	0.9 (0.5)	0.7 (0.5)	UNK	1.2 (0.5)	0.7 (0.5)	0.0 (0.0)	0.9 (0.5)	0.8 (0.5)	NS	NS
Δz-Score[d]	−0.96 (1.12)	−0.52 (0.95)	−0.52 (0.89)	−0.80 (0.59)	UNK	−0.54 (0.83)	−0.86 (0.76)	−0.74 (0.84)	−1.04 (0.86)	UNK	−0.22 (0.74)	−1.08 (0.85)	−2.46 (0.2)	−0.77 (0.90)	−0.92 (0.85)	NS	NS
Head circumference GV																	
cm/week[c]	0.5 (0.4)	0.7 (0.3)	0.6 (0.3)	0.5 (0.3)	UNK	0.5 (0.3)	0.5 (0.3)	0.7 (0.3)	0.5 (0.3)	UNK	0.6 (0.3)	0.3 (0.3)	0.6 (0.4)	0.5 (0.3)	0.5 (0.3)	NS	NS
Δz-Score[d]	−1.19 (1.32)	−0.43 (0.92)	−0.72 (0.79)	−1.18 (0.81)	UNK	−1.32 (0.90)	−1.18 (0.85)	−0.73 (0.93)	−1.09 (0.77)	UNK	−0.75 (1.07)	−1.81 (1.10)	−0.96 (1.26)	−0.97 (1.03)	−1.29 (1.05)	—[a]	NS

NEC																
n (%)	8 (2)	5 (1)	5 (5)	6 (4)	25 (10)	5 (3)	10 (6)	20 (7)	32 (12)	18 (13)	1 (1)	2 (1)	2 (1)	49 (4)	90 (6)	NSNS
NEC scores, Bell II/III	7/0	4/0	5/0	2/4	20/5	3/2	UNK	8/12	26/6	6/12	0/1	2/0	2/0	39/9	47/33	NSNS
Day of NEC onset	12 (9)	11 (8)	11 (12)	15 (9)	14 (11)	27 (18)	25 (9)	18 (16)	23 (16)	17 (15)	13 (–)	20 (10)	8 (1)	13 (10)	21 (15)	—[a]NS
Postconceptional age at NEC onset	225 (20)	214 (12)	215 (15)	228 (15)	221 (13)	203 (28)	215 (14)	202 (17)	217 (15)	199 (15)	221 (–)	226 (6)	235 (7)	221 (16)	210 (18)	—[a]NS
Surgery for NEC, n (%)	0 (0)	0 (0)	0 (0)	3 (43)	5 (20)	3 (60)	5 (50)	10 (50)	8 (25)	11 (61)	1 (100)	0 (0)	0 (0)	8 (16)	38 (42)	NSNS
First stool, DOL	2 (1)	2 (1)	1 (0)	2 (1)	2 (1)	3 (2)	UNK	4 (3)	3 (1)	UNK	3 (2)	1 (1)	2 (1)	2 (1)	3 (2)	—[a] —[a]
Antibiotics																
n (%)	399 (99)	456 (100)	93 (100)	165 (99)	235 (98)	149 (93)	174 (98)	233 (82)	256 (95)	125 (90)	143 (94)	233 (94)	147 (98)	1348 (99)	1460 (92)	—[a] —[a]
Days[b]	19 (12)	12 (10)	25 (13)	23 (13)	16 (10)	11 (12)	13 (12)	12 (11)	13 (12)	8 (9)	7 (7)	8 (8)	16 (9)	17 (12)	11 (11)	—[a] —[a]
Antifungal medicine																
n (%)	59 (15)	109 (24)	12 (13)	65 (39)	29 (14)	148 (93)	76 (43)[e]	9 (3)	28 (10)	34 (81)	112 (74)	18 (7)	35 (24)	274 (21)	384 (29)	—[a]NS
Days[b]	1 (3)	2 (4)	1 (4)	2 (4)	1 (5)	15 (14)	UNK	17 (16)	1 (4)	12 (19)	22 (26)	3 (10)	3 (9)	1 (4)	8 (16)	—[a]ND

Data are presented as mean (SD) unless otherwise stated.

AMS, Academic Medical Center; AUC, University of Auckland and Newborn Service, National Women's Health; BWC, Shenzhen Bao'an Maternal and Child Health Hospital; CHI, Rush University Children's Hospital; COP, University of Copenhagen; DOL, day of life; FOS, Foshan Woman and Children's Hospital; GD, Guangdong province in China; GV, growth velocity; IBA, University of Ibadan and University College Hospital; ND, not done;

NEC, necrotizing enterocolitis; NEW, Newcastle Hospitals NHS Foundation Trust; NICU, neonatal intensive care unit; NS, nonsignificant; PER, University of Western Australia and King Edward Memorial Hospital; PWC, Guangdong Provincial Women & Children's Hospital; SNP, Shenzhen Nanshan People's Hospital; SWC, Shenzhen Maternity & Child Health Care Hospital; TAI, Children's Hospital of China Medical University; TFF, time to full feeding; UNK, unknown.

[a]Significant differences between GD and non-GD, $P < .001$; P_1, unadjusted P-value comparing GD and non-GD units; P_2, P-value comparing GD and non-GD units, adjusted for gestational age.

[b]Deceased infants were excluded from analysis.

[c]

[d]Days 0–28.

[e]All infants with body weight <1000 g received prophylactic fluconazole from birth until the central line was removed.