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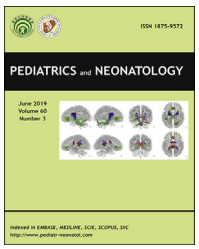

Original Article

Feeding interval and use of donor breast milk for very low birthweight infants: A nationwide survey in Japan

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Background: Enteral feeding is critical for postnatal growth of very low birthweight infants (VLBWI); however, a standard feeding strategy has not been established in Japan. A 2- or 3-h feeding interval is generally used, but no clear evidence supports either approach. Additionally, there is no nationwide breast milk bank in Japan and no consensus exists on the use of donor breast milk (DBM). To clarify the current feeding strategies for VLBWI in Japan, we undertook a nationwide survey.

Methods: We sent a questionnaire to the 382 NICUs included in the Neonatal Research Network in Japan. We sought information on NICU size, number of admissions, necrotizing enterocolitis (NEC) incidence, feeding interval, and use of DBM.

Results: We received responses from 217 NICUs (56.8%), including 76 tertiary centers and 140 regional centers. We only analyzed data obtained from tertiary perinatal centers with a high response rate (77.6%) owing to the insufficient response rate of lower-level facilities (<50%). Most NICUs (71.1%) used a 3-h feeding interval. Only 9.2% used a 2-h interval for all VLBWI. Most NICUs (64.5%) never used DBM, which is not routinely pasteurized. DBM was used in 27 NICUs (35.5%), with and without limitations. Data from 14,233 VLBWI were analyzed; 258 infants (1.8%) were diagnosed with NEC from 2011 to 2015. The incidence of NEC was higher in NICUs that used a 2-h interval (2.7%) than in others. No association was found between NEC and the use of DBM. The NEC incidence did not differ between centers using the most common

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strategy of a 3-h interval without DBM and those using other strategies.
Conclusion: Most NICUs in Japan use a 3-h feeding interval and do not use DBM for VLBWI. Further prospective studies including multiple confounders are required to clarify the relationship between feeding strategy and the incidence of NEC.

1. Introduction

Enteral feeding is critical for the postnatal growth and development of very low birthweight infants (VLBWI; birthweight <1500 g).[1] Several studies have investigated the types of milk used for VLBWI, including fortified versus unfortified, maternal versus donated, and powdered versus liquid formulas.[2,3] Others have evaluated the best time to start enteral feeding[4,5] or the best rate of increasing feeds[6,7] in these premature infants. However, optimal feeding intervals for VLBWI have not been well established. A systematic review reported that "milk feedings can be given via nasogastric tube either intermittently, typically over 10–20 min every two to 3 h, or continuously, using an infusion pump".[8] Therefore, we speculate that these infants are commonly fed every 2 or 3 h worldwide.

In our NICUs, VLBWI are conventionally fed every 2 h (e.g., Kobe University, Tokyo Women's Medical University, and Osaka Women's and Children's Hospital) or 3 h (e.g., Juntendo University and Showa University), with no established evidence. In a previous historical observational study, we compared 2- and 3-h feeding intervals after revising our feeding strategy for VLBWI from every 2 h (12 times a day) to every 3 h (8 times a day) to reduce nursing contacts and unify feeding intervals for all babies. That study revealed that feeding VLBWI every 3 h was comparable to feeding every 2 h with respect to feeding intolerance.[9] This finding indicated that a 3-h feeding interval is feasible for all these vulnerable patients. However, no nationwide data regarding enteral feeding intervals for VLBWI exist in Japan.

Regarding the milk fed to preterm infants, their own mother's milk (OMM) is widely accepted as the first choice for nutrition. Obviously, breast milk has many advantages over artificial formulas as nutrition for newborns. However, the use of donor breast milk (DBM) in cases where the OMM is not available remains controversial. Japan does not have a nationwide human milk bank; thus, it is difficult to get pasteurized DBM when needed. According to a questionnaire survey on the use of DBM for extremely low birth weight infants (birthweight <1000 g) by Mizuno and colleagues, one-fourth of NICUs use DBM for these infants. However, there are no local human milk banks in each NICU, and compliance with internationally published guidelines varies by center. Moreover, the DBM distributed in Japan is freeze–thawed but not pasteurized. Most neonatologists in Japan consider a human milk bank necessary for the treatment of extremely low birth weight infants.[10] However, the use of DBM for VLBWI has not been surveyed until now.

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in neonates, and no single specific preventive strategy exists for NEC. In addition, enteral feeding has been suggested to have a firm association with NEC.[6,11] Henderson et al. performed a multicenter case-control study to elucidate the relationship between enteral feeding practices and the development of NEC in preterm infants; they suggested the duration of trophic feeding and rate of advancement of feeding volumes as risk factors for NEC.[6] However, a Cochrane Review found no evidence that delaying the introduction of progressive enteral feeding or slow increments in feed volume would reduce the risk of NEC in preterm infants.[7,12] Thus, an evidence-based feeding strategy for NEC prevention remains to be elucidated.

Standardization of feeding strategies for VLBWI can be expected to improve outcomes and reduce costs.[13] Intriguingly, Patole et al. reported a significant and prolonged decline in the incidence of NEC after implementation of a standardized feeding regimen.[11] We believe that the standardization of enteral feeding throughout Japan would contribute to better outcomes for VLBWI. Thus, as prerequisite information for a future prospective multicenter study to establish a standard feeding strategy in Japan, we performed a nationwide survey to clarify the current feeding strategies for VLBWI in Japanese NICUs, with a focus on feeding intervals and the use of DBM. In addition, we analyzed the incidence of NEC, to evaluate differences in outcomes among feeding strategies.

2. Methods

A survey of feeding strategies for VLBWI from 2011 to 2015 was sent to all perinatal centers (three level I centers, 281 level II centers, and 98 level III centers) registered in the Neonatal Research Network Japan (NRNJ). Questionnaires were completed by the pediatricians or neonatologists in charge of neonatal care at each institution. Survey questions included (1) the number of NICU beds, (2) the number of Growing Care Unit beds, (3) the use of DBM for VLBWI (a, Routine use; b, No use; c, Use under certain conditions, and what those particular conditions are), (4) the total number of admissions of VLBWI (<1500 g) and infants diagnosed with NEC during the study period, (5) the enteral feeding interval for VLBWI (a, 2-h interval [12 times daily]; b, 3-h interval [8 times daily]; c, at attending physician's discretion; d, other [e.g., 2- or 3-h interval depending on birthweight and/or gestational age, or other]). Regarding query (4), we asked for permission in the questionnaire to obtain patient data from the NRNJ database, which prospectively

registered the clinical information of VLBWI admitted to the participating NICUs.[14,15] NEC was clinically diagnosed and reported according to Bell's criteria as stage ≥2.[16,17] We also included blank space to provide additional information about query (4) in case permission was denied. This survey was conducted after obtaining approval from the ethical committee of Kobe University Graduate School of Medicine. Statistical analyses were performed using chi-square tests for comparisons between two groups. Differences were deemed statistically significant with $p < 0.05$. The collected data were analyzed using descriptive statistics. Values are presented as medians (ranges).

3. Results

3.1. Response rate

The overall response rate for the questionnaire was 56.8% (217/382 centers) (Fig. 1). The response rate was 77.6% (76/98) for level III perinatal centers, 49.8% (140/281) for level II centers, and 33.3% (1/3) for others. Because the response rate of level II perinatal centers and others was very low, we only analyzed the data obtained from level III perinatal centers with a high response rate. The median number of NICU beds among the 76 level III perinatal centers that responded to the survey was 12 (6—51); the median number of Growing Care Unit beds was 18 (6—40).

3.2. Feeding intervals

Regarding enteral feeding intervals, the most common regimen was a 3-h interval, used at 71.1% of centers (54/76). A 2-h interval was used at 9.2% of centers (7/76), regardless of infant condition, whereas 13.2% of centers (10/76) utilized a 2-h feeding interval on the basis of certain conditions, such as birthweight (6/10), gestational age (1/10), or both (3/10). Feeding intervals were not standardized or were based on the attending physician's discretion at 6.6% of centers (5/76)

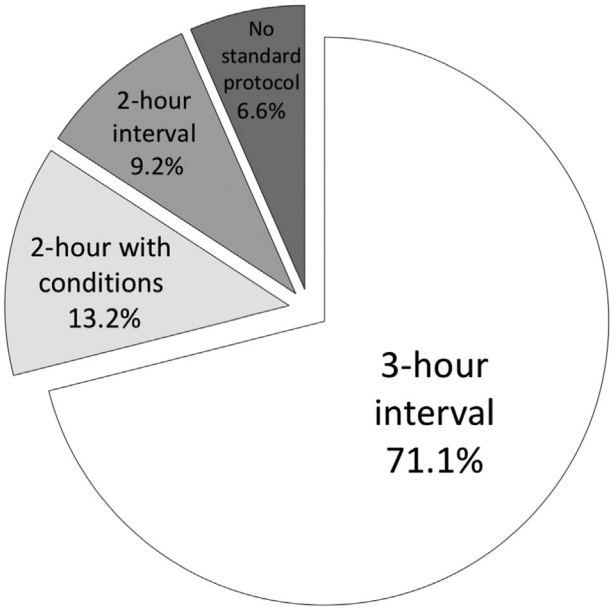

Figure 2 Feeding intervals for very low birthweight infants (VLBWI). A 3-h feeding interval (white) was the most common strategy, followed by a 2-h interval under certain conditions (light gray) and a 2-h interval for all VLBWI (medium gray). No standard protocol was in place at 6.6% of institutions (dark gray).

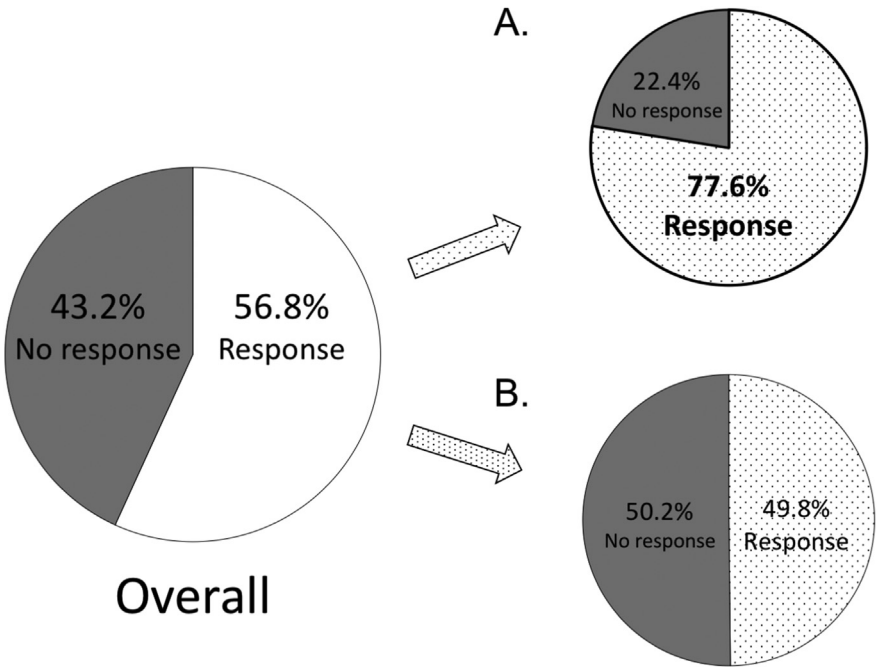

Figure 1 Overall questionnaire response rate and response rates for level III perinatal centers (**A**) and level II perinatal centers (**B**). Responses were received from 76 of 98 level III perinatal centers and from 140 of 281 level II perinatal centers.

(Fig. 2). We investigated the location of NICUs according to feeding interval and found that NICUs using a 2-h feeding interval for VLBWI were all located in western Japan (Fig. 3A).

3.3. Donor breast milk use

Breast milk donated from other mothers was never used at 64.5% (49/76) of centers. DBM was used at 23.7% of centers (18/76) without any conditions and at 11.8% of centers (9/76) under certain conditions. These conditions included birthweight (e.g., <1000 g at 1/9 centers), gestational age (e.g., ≤28 wk at 5/9 centers), or other (e.g., babies with NEC or whose mothers carry human T-lymphotropic virus 1 at 3/9 centers) (Fig. 4). When we evaluated the use of DBM according to clinic location, we found that the NICUs in which DBM was used were distributed evenly across the country (Fig. 3B).

3.4. Total VLBWI admissions and number of infants diagnosed with NEC

Most NICUs (94.7%, 72/76) permitted data extraction from the NRNJ database. We obtained complete admission data for the 5-year period from 53 NICUs (69.7%) of the 76 level III perinatal centers that responded to the questionnaire; the remainder provided partial data. A total of 14,934 VLBWI were admitted to NICUs that responded to this survey; 701 patients without data concerning feeding strategy or NEC were excluded from further analysis. Thus, we analyzed the data of 14,233 infants; 258 of these (1.8%) were diagnosed with NEC during the study period.

3.5. Incidence of NEC according to feeding strategy

Regarding the incidence of NEC according to feeding interval, the NEC incidence was higher at centers that fed every 2 h (2.7% of infants, 35/1300) than among those that fed every 3 h, with marginal significance (1.9% of infants, 188/9,947, $p = 0.051$), and those that fed according to other strategies, with significance (1.2%, 35/2,986, $p < 0.001$; Table 1). Regarding the use of DBM, the NEC incidence was 1.7% (109/6247) at clinics that used DBM with or without conditions and 1.9% (149/7986) at those that never used DBM ($p = 0.592$; Table 1). The questionnaire revealed that a 3-h interval without use of DBM (42.6%) was the most common feeding strategy in Japan. Therefore, we compared the incidence of NEC between facilities using a 3-h interval without DBM versus the others. The incidence of NEC was 2.0% (124/6070) at facilities using the most common strategy (3-h interval without

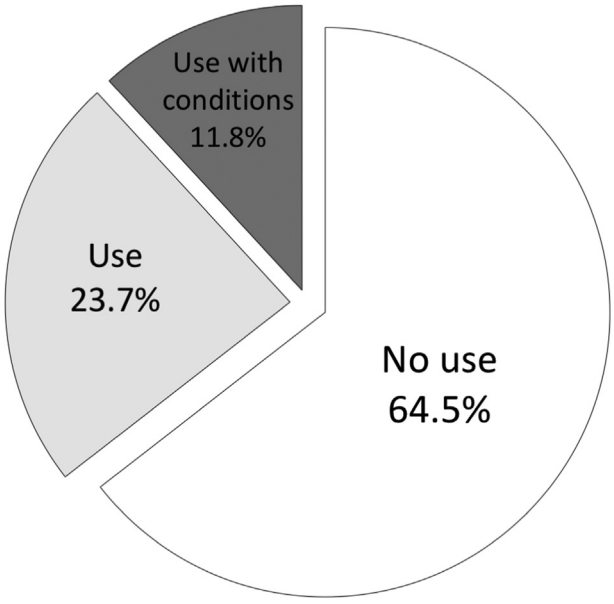

Figure 4 Use of donor breast milk (DBM) for very low birthweight infants. Non-use of DBM (white) was the most common strategy, followed by use of DBM (light gray), and conditional use of DBM (dark gray).

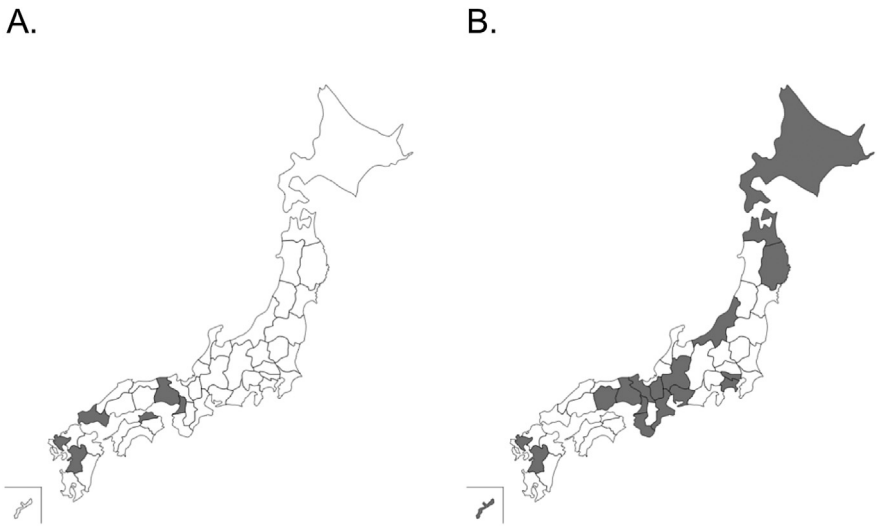

Figure 3 Location of NICUs that use a 2-h interval strategy (**A**) and donor breast milk (**B**) for very low birthweight infants in Japan. Prefectures that contain at least one NICU that uses a 2-h feeding interval (**A**) or donor breast milk (**B**) are shown as gray regions on the map.

Table 1 Incidence of necrotizing enterocolitis, according to feeding strategy.

	Feeding Strategy	Number of NEC patients	Number of VLBWI	NEC incidence (%)	P-value
Interval	Every 2 h	35	1300	2.7	Reference
	Every 3 h	188	9947	1.9	0.051[a]
	Other	35	2986	1.2	<0.001[a]
DBM	Use	109	6247	1.7	Reference
	No use	149	7986	1.9	0.592[b]
Every 3 h without DBM	Yes	124	6070	2.0	Reference
	No	134	8163	1.6	0.076[c]

Abbreviations: DBM, donor breast milk; NEC, necrotizing enterocolitis; VLBWI, very low birthweight infants.
[a] vs. 2-hour feeding interval.
[b] vs. DBM use.
[c] vs. 3-hour interval without DBM.

DBM) and 1.6% (134/8163) at facilities using other strategies; this difference was not significant ($p = 0.076$; Table 1).

4. Discussion

This is the first nationwide survey concerning enteral feeding strategies for VLBWI in Japan. We found that most NICUs in Japan use a 3-h feeding interval for VLBWI, but that a 2-h interval is predominant in western Japan. According to our study, the use of DBM for VLBWI is uncommon in Japan; only 36% of NICUs used DBM with or without limitations.

The incidence of NEC was higher at facilities using a 2-h feeding interval than at facilities using other feeding intervals; no association was found between NEC and the use of DBM. NEC incidence did not differ between centers using the most widely used feeding regimen (every 3 h without DBM) and those using other regimens.

This survey revealed regional differences in feeding intervals. This regional difference might result from historical tradition because until now, there has been no established evidence for the benefits of any feeding interval. Each feeding strategy has its own advantages and disadvantages. For example, the 2-h feeding interval, which uses a smaller volume of milk per feeding, is regarded as useful to prevent gastroesophageal reflux by avoiding over-dilation of the stomach.[9] In addition, Maruyama and colleagues reported that the volume of milk per feeding is associated with a postprandial increase in blood flow velocity through the superior mesenteric artery, as seen with pulsed Doppler ultrasound, suggesting that a shorter feeding interval with a smaller volume per meal is preferable to prevent dynamic postprandial changes in intestinal blood flow.[18] In contrast, a 3-h feeding interval is superior for preventing intestinal blood flow congestion after feedings[19] and seems more physiologically sound for the digestive system of preterm infants because gastric emptying takes approximately 3 h in these patients.[20] The main concerns with adopting a 2-h feeding interval for VLBWI are the increased risk of medical accidents, such as erroneous administration to the wrong patient or forgetting a feeding because of the existence of two different feeding intervals (2-h feeding interval for infants <1500 g and 3-h interval for infants >1500 g). In addition, almost any type of intensive care procedure performed in the NICU can provoke peak blood pressure increases and transcutaneous PO_2 decreases in VLBWI.[21] Therefore, frequent procedures, including feedings every 2 h, increase the risk of complications such as intraventricular hemorrhage in these tiny babies. Intriguingly, this survey also showed that the NEC incidence was higher at facilities with a 2-h feeding interval than at those with other feeding intervals. Regarding mechanisms of the differences in NEC incidence between the feeding intervals, we found that the number of VLBWI admissions per NICU during the study period at centers following other feeding intervals (230, 2986/13 centers) was higher than those at centers following 2-h (186, 1300/7 centers) or 3-h (184, 9947/54 centers) intervals, despite no difference in the number of NICU beds between the centers (other, 12 (9—21); 2-h intervals, 12 (6—51); and 3-h intervals, 12 (9—18)). Thus, we speculate that the superior expertise in VLBWI care of the centers with other feeding intervals could affect the reduced NEC incidence in this survey.

In our previous observational study, we reported the impact of a clinical policy change from a 2-h to a 3-h feeding interval for VLBWI. We concluded that there was no significant difference with respect to the establishment of enteral feeding between the two regimens, but we found that the incidence of chronic lung disease was higher with the 2-hourly feeding regimen.[9] Recently, Ibrahim et al. performed a randomized controlled trial comparing 2-h and 3-h feeding intervals for VLBWI and reported no significant differences between the regimens regarding the time required to reach full feedings or the incidence of clinical morbidities such as NEC, gastroesophageal reflux, feeding intolerance, hypoglycemia, ketonuria, neonatal jaundice, or death.[22] Thus, it is possible that feeding intervals for VLBWI will converge at a 3-h interval. For standardization of feeding intervals in Japan, more concrete evidence, including a multicenter prospective randomized controlled trial, is necessary.

Early aggressive nutrition has recently been postulated as important for physical and mental development in preterm infants.[23,24] In a single-center study at a facility that used DBM, early enteral feeding that was started within 24 h after birth was associated with a decreased incidence of NEC and death.[25] In addition, in their population-based study, Kantorowska and colleagues reported that the availability of DBM was associated with positive changes,

including increased breast milk feeding at NICU discharge and decreased NEC rates.[26] In terms of nutritive value and risk of NEC, OMM is far superior to formula milk. However, the availability of OMM for intensive nutrition management within 24 h after birth is a challenge for these very premature infants. Because of the infection risk, use of DBM remains controversial in cases where OMM is unavailable. According to the 2011 questionnaire survey by Mizuno and colleagues, only 35% of NICUs initiated the first enteral feeding by 24 h of age; 17% of NICUs did not initiate enteral feeding until OMM was available.[10] This finding suggests that unavailability of OMM delays the initiation of enteral feedings for these preterm infants, who are susceptible to feeding intolerance. According to our data and those of Mizuno et al., most NICUs in Japan do not use DBM.[10] In addition, an observational study including two tertiary centers in Japan clarified that the prevalence of exclusive breastfeeding among low birth weight infants was 22.6% at NICU discharge.[27] To promote early enteral feeding for VLBWI, discussion of establishing a national milk bank in Japan to provide safer DBM is warranted.

A limitation of the present study is the very low overall response rate for the questionnaire; hence, we could not include the data of level II perinatal centers and other centers in the additional analysis. Thus, the result of our study only represents the clinical practice for VLBWI of tertiary centers and cannot be generalized to all NICUs in Japan. On the other hand, the response rate of level III perinatal centers (77.6%) was high, considerably higher than those of other recent nationwide surveys in Japan, such as 70.7% in a survey of the need for human milk banking,[10] 64% for clinical kernicterus in preterm infants,[28] 62.3% for neonatal transportation practices,[29] and 57.7% for neonatal gastrointestinal perforation.[30] In addition, a total of 14,934 VLBWI admitted to the level III perinatal centers that completed our questionnaire accounted for 69.4% (14,934/21,518) of the VLBWI admitted to all perinatal centers responding to this survey. Another limitation of this study is that we did not assess data about feeding intolerance because it is difficult to uniformly evaluate feeding intolerance using a questionnaire. Therefore, we evaluated the incidence of NEC at each NICU as a substitute. Ibrahim et al. reported that the incidence of feeding intolerance (gastric residual >25% of the previous feeding volume) did not differ with the use of 2- versus 3-h feeding intervals.[22] The incidence of feeding intolerance is an important factor when determining a suitable nutritional approach, and thus should be considered in future studies. Furthermore, we did not analyze factors contributing to the development of NEC other than feeding intervals and the use of DBM, such as antibiotic use/duration, probiotic use, and H_2 blocker use, owing to a lack of information in the database. In addition, to adequately evaluate the impact of the bolus feeding interval, other differences in the feeding protocol such as volume of daily increment and prior use of minimal enteral feeding should be considered.[31] Finally, we must emphasize that this study examined the policies of feeding strategies for NICUs in Japan but not the actual feeding practices in individual cases. Further prospective studies including detailed patient background and patient care information are required to clarify the relationship between feeding strategy and incidence of NEC.

In conclusion, our nationwide survey found that most NICUs in Japan use a 3-h feeding interval for VLBWI, but a 2-h feeding interval is predominant in western Japan. The use of DBM for VLBWI is uncommon in Japan. Although the incidence of NEC at centers with a 2-h feeding interval was higher than that at centers using other strategies, it is difficult to conclude that NEC is associated with a 2-hourly feeding strategy because this is fundamentally a survey of one aspect of feeding; the issue is very complex and the confounders very important. Further multicenter prospective studies are necessary to establish standard protocols in Japan.

Conflicts of interest statement

The authors declare no conflicts of interest.

Acknowledgments

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