CE 1.5 HOURS Continuing Education

Feeding Intervals in Premature Infants ≤1750 g

An Integrative Review

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ABSTRACT

Background: The timely establishment of enteral feeds and a reduction in the number of feeding interruptions are key to achieving optimal nutrition in premature infants. Nutritional guidelines vary widely regarding feeding regimens and there is not a widely accepted consensus on the optimal feeding interval.

Purpose: To critically examine the evidence to determine whether there is a relationship to feeding intervals and feeding outcomes in premature infants.

Methods: A systematic review of the literature in the following databases: PubMed, CINAHL, Embase and the Cochrane Library. The search strategy used the terms infant premature, low birth weight, enteral feeding, feed tolerance and feed intervals.

Results: Search results yielded 10 studies involving 1269 infants (birth weight ≤1750 g). No significant differences in feed intolerance, growth, or incidence of necrotizing enterocolitis were observed. Evidence suggests that infants fed at 2 hourly intervals reached full feeds faster than at 3 hourly intervals, had fewer days on parenteral nutrition, and fewer days in which feedings were withheld. Decrease in the volume of gastric residuals and feeding interruptions were observed in the infants fed at 3 hourly intervals than those who were continuously fed.

Implications for Practice: Reducing the feed interval from 3 to 2 hourly increases nurse workload, yet may improve feeding outcomes by reducing the time to achieve full enteral feeding.

Implications for Research: Studies varied greatly in the definition and management of feeding intolerance and in how outcomes were measured, analyzed, and reported. The term "intermittent" is used widely but can refer to a 2 or 3 hourly interval.

Key Words: feed interval, feed intolerance, feed schedule, low birth weight, premature infant

Nutrition is fundamental to the management of premature infants. Yet, meeting the nutritional demands of this population poses challenges to caregivers. Due to gut immaturity and additional complications associated with prematurity, initial nutritional demands cannot be met by enteral means alone. However, the timely establishment of full enteral nutrition is imperative to avoid complications associated with vascular access, sepsis, and adverse effects of parenteral nutrition.[1] Feeding intolerance in the premature infant is frequently manifested as an inability to digest enteral feedings and is associated with increased gastric residuals, abdominal distension, and emesis.[2,3] Extremely premature infants often demonstrate feeding intolerances, and due to their propensity to develop necrotizing enterocolitis (NEC), the threshold for withholding or withdrawal of feeds is extremely high in this population.[4] The negative impact from a lack of enteral nutrition can compound intestinal dysfunction, leading to high morbidity and mortality.[5,6] Establishing full enteral feeds can vary in duration between individual patients but is expected to take up to 2 weeks in infants weighing ≤1000 g, and 1 week in infants weighing between 1000 and 1500 g, but can take several weeks depending upon the infant's health status.[7]

Despite the benefits of establishing full enteral feedings early, no clear relationship between the feeding interval and feeding intolerance has been established, and nutritional guidelines vary widely regarding the optimal feeding intervals. This fact was highlighted recently in a survey by Klingenberg et al[8] on international enteral feeding practices, which revealed marked variations in feeding intervals among infants <28 weeks' gestation. They found that 38% of neonatal units reported using continuous and hourly feeds, 35% of units reported using a 2 hourly interval, 9% reported an hourly interval, and other was 20%.[8] A Cochrane systematic review compared a continuous feeding interval with an intermittent interval in very low

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birth-weight (VLBW) infants. In this review, intermittent feeding intervals included those infants fed at either 2 or 3 hourly intervals. The meta-analysis from the Cochrane review revealed no significant difference in days to full feeds between the continuous and intermittent feeding methods, although the authors acknowledge that significant statistical heterogeneity existed, suggesting the studies may have assessed this outcome differently.[9] The purpose of this integrative review was to examine all the available clinical evidence to determine whether any relationship exists between a particular feeding interval and feeding outcomes in premature infants. Any such finding would be significant in determining an optimum feeding interval for premature infants establishing enteral feedings and could result in more standardized feeding practices.

OBJECTIVES

The primary outcome of this review was to examine the influence of feeding interval during the establishment of enteral feedings in premature low birth-weight infants on feeding outcomes. Trials that compared feeding intervals in premature infants were reviewed for the following parameters: feeding intolerance as measured by duration to establish full enteral feeding, feeding interruptions, gastric residual volumes, and days on parenteral nutrition. Secondary outcomes, which may be influenced by the feeding interval, were assessed using the following parameters: growth utilizing weight, incidence of NEC-Bells Stage 11 criteria,[10] and mechanical ventilation.

SEARCH METHODS

A systematic search of feeding trials in low birth-weight infants was conducted. Studies that compared feeding intervals from the initiation of feedings until infants were tolerating full feedings, incorporating a continuous interval or either 2 or 3 hourly intermittent intervals, were included. Randomized controlled trials (RCTs), quasicontrolled and cohort studies were included. Due to the paucity of research trials on this subject, the review did not limit itself to VLBW infants; rather an upper birth weight limit of 1750 g was used. Search terms were identified through the thesauri of the databases searched and from the terminology used in articles identified. Search terms used were medical subject headings (MeSH): low birth weight, feeding intervals, enteral feeding, feeding intolerance, and feeding outcomes. Databases searched included Embase, PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Library. Both Google Scholar and the Web of Science citation index were used for citation searches, as were the reference lists of abstracted articles. The central register for clinical trials was searched via the Cochrane library and Clinical trials.gov. Gray literature using "Lenus" was searched for reports, dissertations, and academic reports not published commercially. No limits were applied in relation to year of publication or language. The authors engaged in face-to-face meetings to resolve any difference of opinion on suitable studies for inclusion/exclusion. Thirty articles were assessed and screened for eligibility, from which 12 were identified for possible inclusion. Following a detailed full-text examination, an additional 2 were excluded from the review. These were excluded as one used an hourly interval in the intermittent group[11] and one combined the data from 2 and 3 hourly interventions in the intermittent group.[12] The search process is demonstrated in Figure 1, and characteristics of excluded studies are shown in Table 1.

DATA EXTRACTION

Data from the selected studies were sorted into individual tables, with reference to authors, study settings, geographical location, research question/aim/objectives, inclusion/exclusion criteria, sample size, patient characteristics, methodology, feeding protocols, feed intolerance protocols, randomization processes, intervention details, outcome measures, analysis, results, conclusions, and recommendations.

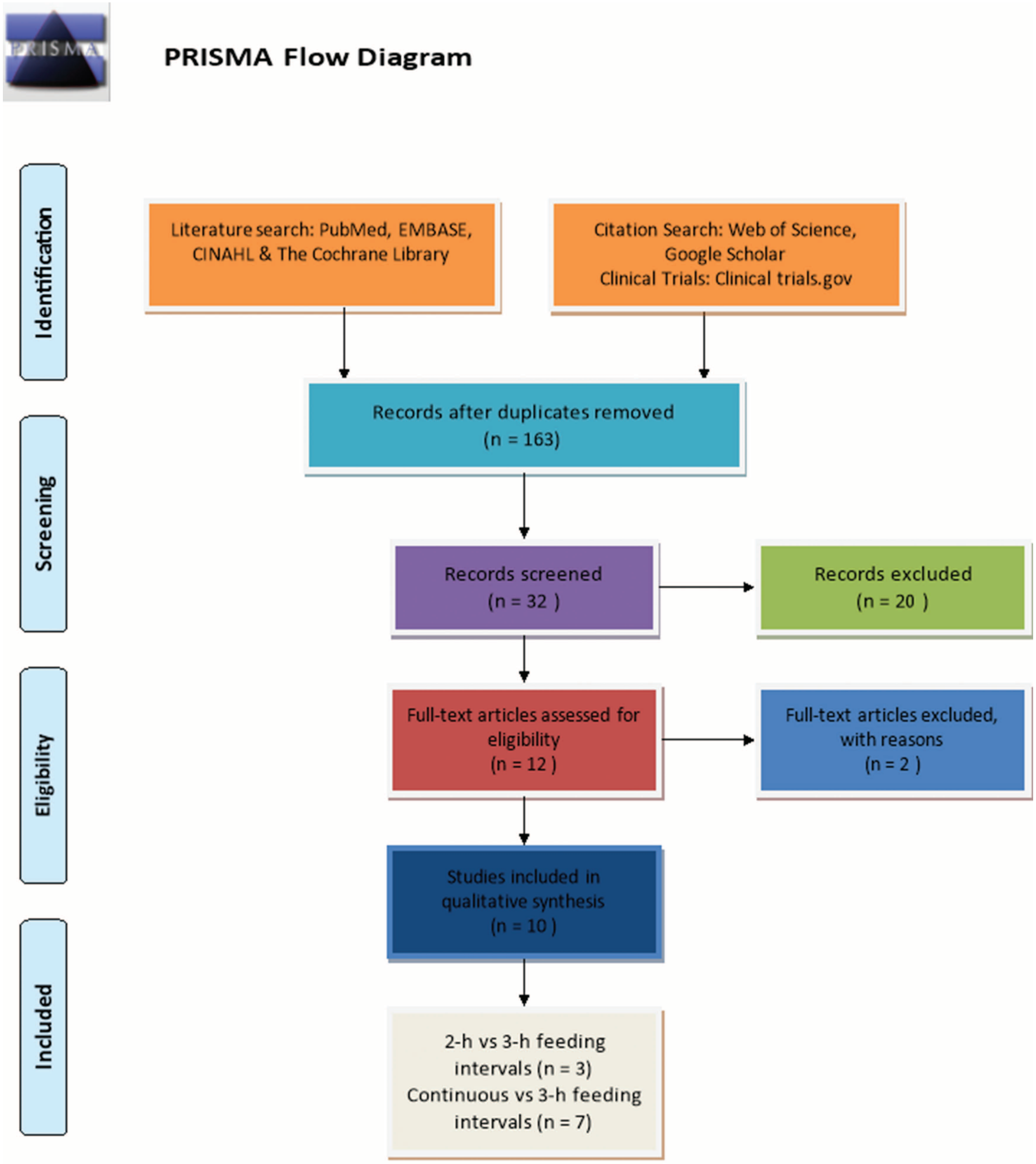
DATA ANALYSIS

Ten studies were selected for inclusion in the review, which, when combined, provided data on 1269 infants.[14-23] Articles were narratively summarized, giving an overview of the study design, sample size, methodology, intervention, and summary of the results. This was followed by quality analysis and synthesis. Three studies compared a 2 hourly interval with a 3 hourly interval.[15,16,20] Seven studies compared an intermittent (3 hourly interval) with a continuous interval.[14,17,19,21-23] No studies were identified that compared a 2 hourly interval with a continuous interval. The characteristics of included studies are displayed in Table 2. Three hourly feeding intervals were given to 716 (56%) infants, the continuous interval was used in 362 (28%), and a 2 hourly interval was used in 191(15%) infants, as depicted in Table 3. Birth weight demographics and gestational ages of included cases are depicted in Table 4.

QUALITY APPRAISAL OF INCLUDED STUDIES

Quality appraisal of the RCTs was conducted using the Review Manager tool, a computer program created by the Cochrane review (RevMan) 5.3.[24] Potential biases from including older studies were evaluated, as current approaches to neonatal care have led to standardized feeding regimens, the use of antenatal steroids and a greater awareness of the advantages

FIGURE 1



PRISMA flowchart[13] preferred reporting items for systematic reviews and meta-analysis: the PRISMA statement. Permission granted for reuse.

of using human milk rather than formula.[25,26] All the studies were conducted in an acute hospital setting and all but one were conducted within the past 20 years.[23] Issues of bias identified were as follows:

- *Selection bias (randomization)*. Of the 10 studies included in the review, 7 were randomized.[14,16,17,19,21-23]
- *Selection bias (allocation)*. One study used alternate assignment.[23] Six studies used blinding of allocation with sealed opaque envelopes.[14,16,17,19,21,22]
- *Performance bias (outcome)*. It was not feasible to blind caregivers to the intervention in any of the selected studies. Blinding of outcome assessors was difficult to ascertain; 1 study reported that radiographic assessors were blinded for the outcome of NEC.[21]
- *Incomplete outcome data*. Complete follow-up was demonstrated among all studies. All of the studies reported on dropouts and loss to follow-up. Feed intolerance was the main reason that led to infants switching feeding methods. These infants were excluded from follow-up.

TABLE 1. Excluded Studies

Excluded Studies	Reason for Exclusion
Dollberg et al,[12]	Intermittent group fed by bolus every 2 h in birth weight 501-750 g and every 3 h in birth weight 750-1250 g. Data from these groups were combined for analysis. It was not possible to differentiate outcomes for 2 or 3 hourly interventions separately
MacDonald et al,[11]	Intermittent interval was hourly. Review criteria included continuous, 2, or 3 hourly only

- *Interventions*. Feeding protocols were predetermined in the RCTs and could not be predefined in the observational studies. The type of milk varied in all studies, and no studies were limited to human milk. In the continuous feeding groups, feeds were administered via an infusion pump. The study by Rovekamp-Abels et al[19] differed in that continuous feeds were administered by gravity, with the syringes being topped up with milk every 15 minutes throughout the day. All the intermittent bolus feeds, 2 and 3 hourly, were administered by gravity in an open syringe. Feeding tubes mostly favored the nasogastric route, and the orogastric route was used in 2 studies.[16] A summary of the risk of bias outcomes is displayed in Figures 2 and 3.

RESULTS

Outcome Measures: Primary Outcomes

Duration to Full Enteral Feedings

Feeding intolerance, as measured by time per day to achieve full enteral feeds, was measured in 9 of 10

TABLE 2. Characteristics of Studies Included in the Review

Study	Intervention	Results Summary
Akintorin et al,[14] RCT	Continuous feeds by pump, bolus feeds every 3 h	No significant difference in days to full enteral feeds or in feed intolerance in either group
DeMauro et al,[15] Retrospective cohort	Bolus feeds of 2 or 3 hourly intervals	Infants fed at 2-h intervals reached full feeds 2.7 d sooner than at 3-h. Infants fed 3-h more likely to have >28 d of parenteral nutrition and have feeds held for >7 d
Dhingra et al,[16] RCT	Bolus feeds of 2 or 3 hourly intervals	No difference in feed intolerance, apnea, or hypoglycemia in either group. More nursing time feeding 2-h than 3-h
Dsilna et al,[17] RCT	Continuous feeds by pump, bolus feeds every 3 h to either nasogastric or orogastric groups	Continuous fed group reached full feed faster than 3-h interval, hazard ratio 1.86; 95% CI. Continuous fed group had better growth rate ($P = .002$)
Rojahn and Lindgren,[18] Retrospective cohort	Continuous feeds by pump, bolus feeds every 3 h	Continuous fed group reached full enteral feeding faster than 3- h interval
Rovekamp-Abels et al,[19] RCT	Continuous feeds topped up by hand every 15 min, bolus feeds every 3 h	No difference in days to full enteral feeding. Gastric residual volumes were lower in 3-h interval group, 0.9 mL/d, as was the total number of feed interruptions 76 vs 59 (16%)
Rudiger et al,[20] Retrospective cohort	3 Bolus feeds of 2 or hourly intervals	Time to reach full enteral feeds in 2-h 26 (7-69) vs 3-h 20 (12-58) not clinically significant. No difference in weight gain. Duration of phototherapy and nCPAP significantly longer in 3-h than 2-h group ($P \leq .01$)
Schanler et al,[21] RCT	Infants were ≥96 hours and fed continuously or bolus 3 hourly by naso- or orogastric tube	Time to full oral feeding similar. Bolus group had less feeding intolerance and greater rate of weight gain than continuous group
Silvestre et al,[22] RCT	Infants fed continuously over a 3-h period or bolus every 3 h	No significant difference in days to reach full enteral feeding, birth weight, or discharge
Toce et al,[23] RCT	Continuous feeds by pump, bolus feeds every 3 h by naso gastric tube	Continuous feeding associated with a significant increased weight gain of 3.6 g/kg/d in the 1000g-1250g BW

Abbreviations: BW, birth weight; CI, confidence interval; nCPAP, nasal continuous positive airway pressure; RCT, randomized controlled trial.

TABLE 3. Total Participants in Each Intervention

Study	2 Hourly	3 Hourly	Continuous
Akintorin et al,[14]	–	41	39
DeMauro et al,[15]	103	251	–
Dhingra et al,[16]	46	46	–
Dsilna et al,[17]	–	46	22
Rojahn and Lindgren[18]	–	24	25
Rovekamp-Abels et al,[19]	–	125	121
Rudiger et al, [20]	42	32	–
Schanler et al,[21]	–	88	83
Silvestre et al,[22]	–	40	42
Toce et al,[23]	–	23	30
Total	*191*	*716*	*362*

studies.[14-22] There was substantial variability in the definition of full feeds among the studies, ranging from 100 up to 180 mL/kg/d, making a comparison difficult, displayed in Table 5. Days to full feeding refers to the time it takes an infant to progress from the initiation of enteral feeding to tolerating a sufficient quantity without the need for additional parenteral nutritional support, around 120 mL/kg/d.[1] Significant heterogeneity existed due to variations in the initiation of feeds, the rate of advancement of feeds, type of milk, and management of feeding intolerance. In 6 studies, feeds were introduced within 12 hours after birth,[14-16,20,21] within 24 hours in 2 studies,[18,19] within 30 hours in 1 study,[17] and

TABLE 4. Demographic Details—Birth Weight, Average Gestational Age

Study	BW, g	Mean BW, g	AGA
Akintorin et al,[14]	<1250	995	28.9
DeMauro et al,[15]	<1500	1053 (q 2h)	28.3
		1204 (q 3h)	29.6
Dhingra et al,[16]	<1750	1249	31.6
Dsilna et al,[17]	<1200	850	26.8
Rojahn and Lindgren[18]	<1250	860	27.0
Rovekamp-Abels et al,[19]	<1750	1069	28.5
Rudiger et al,[20]	<1000		26.9
Schanler et al,[21]	<1250	1032	28.1
Silvestre et al,[22]	<1500	1121	27.0
Toce et al,[23]	<1250	1239	30.9

Abbreviations: AGA, average gestational age; BW, birth weight.

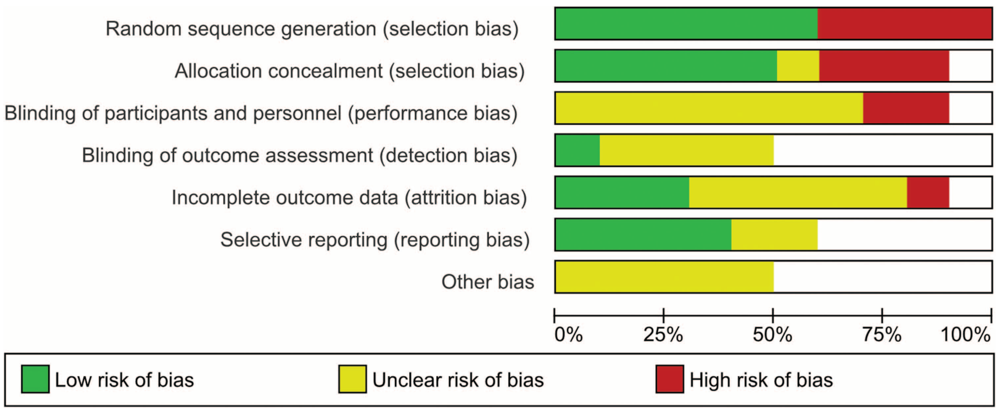
day 2 or 3 in 1 study.[22] The oldest study included conducted by Toce et al[23] did not enter infants into the trial until deemed ready to start feeds and no longer receiving ventilator support, around day 7. In 1 retrospective study, trophic feeds of <20 mL/kg/d were introduced and duration to full feeding was measured once feeds were advanced.[15] The study by Schanler et al[21] randomized infants to receive 1 of 4 treatment options, the presence or absence of gastrointestinal priming for 10 days plus continuous or intermittent bolus feeding.

Reflecting the diversities in practice, the time to achieve full enteral feeding varied between studies, but was similar among feeding intervals, as shown in Table 6. Three studies reported >20 days to achieve full enteral feeds in both intervention groups.[17,20,21] Three out of 10 studies compared a 2 hourly interval with a 3 hourly interval.[15,16,20] In 1 observational study, infants fed at 2 hourly intervals achieved full enteral feeding 2.7 days sooner that at 3 hourly intervals. In bivariate and multivariate analysis, infants <28 weeks' gestation reached full feedings 7.2 days (95% confidence interval [CI], 1.5-12.9 days) sooner on 2 hourly intervals than 3 (P = .014).[15] Neither of the other 2 studies that compared a 2 hourly with 3 hourly intervals observed a significant difference in days to attain full feeding.[16,20] Studies that compared an intermittent interval (3 hourly) versus a continuous method had conflicting outcomes on days to full feedings. Three studies found no difference in days to full feedings between the continuously fed or 3 hourly interval subjects.[14,19,22] Infants in 1 study took significantly longer to achieve full feedings if fed by the continuous feeding method.[21] Yet, 2 studies reported a better outcome in infants fed continuously.[17,18] In one of these studies, continuously fed infants achieved full feedings significantly faster than infants fed at 3 hourly intervals, an average of 20 days versus 26 days (hazard ratio = 1.86; 95% CI, 1.07-3.22).[17] This duration to full feedings is considerably longer than that reported by other studies in this review (10-12 days), thus limiting the applicability of this finding.

Sub Group Analysis

Subgroup analysis based upon birth weight was performed by 4 studies.[14,15,19,21] The incidence of feeding intolerance correlated with a lower gestational age and birth weight. Those most at risk of feeding-related complication are the smaller and most premature infants.[27,28] Comparing a 2 hourly with a 3 hourly intervention, the study by DeMauro et al[15] reported that, in both the bivariate and multivariate analyses, the effect of feeding interval was greatest among the lower gestational age group. Infants <28 weeks reached full feedings 7.2 days (95% CI, 1.5-12.9 days) sooner on 2 hourly intervals than on 3 hourly intervals.[15] The

FIGURE 2



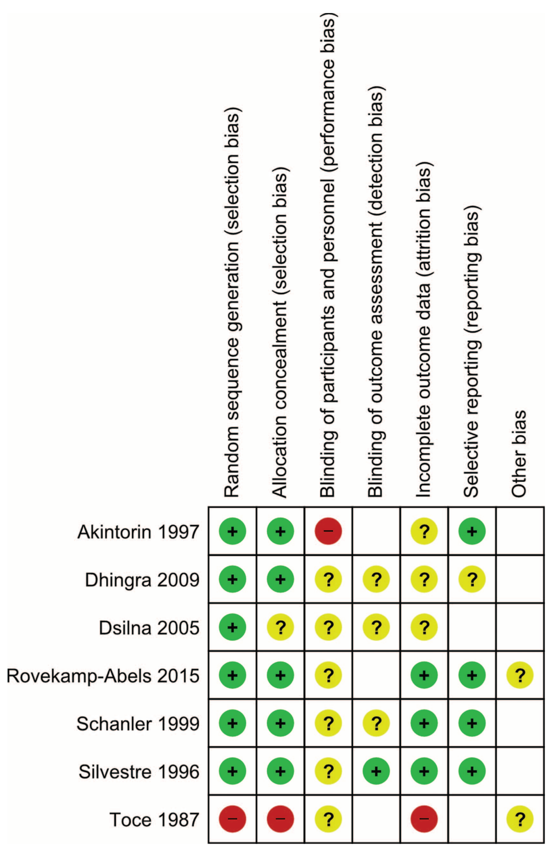
Risk of bias graph, included randomized controlled trials.[24]

other 3 studies reported a higher rate of feeding intolerance, presenting with an increase in residuals in the smaller infants.

Feeding Interruptions

Feeding intolerance as measured by feed interruptions was reported in 7 out of 10 studies.[14-17,19-21]

FIGURE 3



Risk of bias summary diagram, included randomized controlled trials.[24]

Infants fed by continuous rates had higher incidences of feeding intolerance associated with gastric residuals than those fed 2 or 3 hourly. Decisions to pause or withhold feedings were based upon increase in gastric residuals by more than or equal to the previous feeding volume,[20] greater than 33% of previous feeding volume,[16] greater than 50% volume of previous feeding volume,[17,18] greater than 3-fold the hourly volume or exceeded the volume of the preceding bolus or continuous feed volume,[19] greater than 2-mL undigested formula in the intermittent group, or the volume of 2 hours in the continuous group.[22] One study developed a guideline to determine excessive residuals as follows: greater than 50% the volume of the proceeding feed in the 3 hourly intermittent intervals. Yet, the same study for the continuous interval defined an excessive residual as 2.5 times the hourly volume when the infusion rate was 2 mL/h; 1.5 times when the rate was 2 to 3 mL/h; more than the hourly rate when the infusion rate was 3 to 5 mL/h, or more than half when the rate was 5 mL/h.[14] What volume would be deemed excessive was not clarified in the remaining 3 studies.[14,21,23] In addition, abdominal distention was considered to be a feature of feeding intolerance.[17,20-23] Two studies further defined abdominal distention by increase in girth by more than 2 cm in 6 hours[14] or more than 2 cm in 12 hours.[16] Additional signs of feeding intolerance, which may either alone or in the presence of more than 1 symptom, lead to withholding of feeds-included bloody stools, dilated loops of bowel, increase in apneas and bradycardias, and a suspicion of NEC.

In the study by DeMauro et al,[15] feed interruptions of over 1 week due to feeding intolerance, sepsis, hypotension, and medical or surgical treatment of a patent ductus arteriosus were more common in infants fed at 3 hourly rather than 2 hourly intervals (OR = 4.7; 95% CI, 1.9-11.7). While Akintorin et al[14] reported no

TABLE 5. Definition of Full Feeds

Study	Definition of Full Feeds
Akintorin et al,[14]	100 kcal/kg/d
DeMauro et al,[15]	120 mL/kg/d
Dhingra et al,[16]	150 mL/kg/d
Dsilna et al,[17]	140-160 mL/kg/d
Rojahn and Lindgren[18]	120 and 150 mL/kg/d
Rovekamp-Abels et al,[19]	120 mL/kg/d
Rudiger et al,[20]	140 mL/kg/d
Schanler et al,[21]	150 mL/kg/d
Silvestre et al,[22]	75 cal/kg/d
Toce et al,[23]	180 mL/kg/d

difference in the incidence of feeding intolerance (14 [n = 39] continuous vs 14 [n = 41] 3 hourly), the indication to interrupt feeding differed according to the feeding interval. Infants fed continuously experienced more feeding interruptions due to excessive residuals, while those fed at 3 hourly intervals were more likely to have feeds withheld due to apneas and bradycardias (incidence not reported). The study used a different threshold for the management of gastric residuals in each intervention as described earlier, which may have confounded the results.[14] Feeding interruptions due to increased residuals occurred more frequently among continuously fed infants than those fed 3 hourly in the most recently published RCT by Rovekamp-Abels et al.[19] Feed interruptions were experienced by 63% of infants fed continuously, compared with 47% of infants who were fed at a 3 hourly interval. In a subgroup analysis of infants ≤1000 g, the incidence of feed interruptions rose to 82% among those fed continuously and 67% in those fed at 3 hourly intervals.[19]

In contrast, the RCT by Dhingra et al[16] comparing 2 hourly and 3 hourly interventions found no difference in feed intolerance, apnea, or hypoglycemia. In the subgroup analysis of infants ≤1250 g, there was a trend toward less feeding intolerance in the 3 hourly intervention group (5 of 28 vs 7 of 22), although the mean time to reach full enteral feeding was not different.[16] No differences among the feeding intervals resulting in feeding interruptions were noted in 4 studies.[14,20,21,23]

TABLE 6. Primary Outcome—Days to Full Feeding, 9 of 10 Studies[a]

Study ID	N	2 Hourly[b]	N	3 Hourly	Difference
DeMauro et al,[15] SD	103	6.7 (3.2)	251	9.4 (8.6)	$P \leq 0.001$
Dhingra et al,[16] SD	43	8.1 (5.9)	44	8.1 (3.9)	$P = 0.492$
Rudiger et al,[20] range	42	26 (7-69)	32	20 (12-58)	$P = 0.15$
	N	**3 Hourly[c]**	**N**	**Continuous**	
Akintorin et al,[14] SD					
700-1000g	23	18 (5.4)	17	19.7 (6.7)	
1001-1250g	18	12.4 (3.9)	22	13 (5.2)	
Dsilna et al,[17] SD					
Nasogastric	22	26.1 (13.6)	22	20.1 (10.5)	$P = .027$
Orogastric	24	28.8 (18.2)			
Rojahn and Lindgren,[18] range	24	12 (4-27)	25	9 (2-25)	$P = 0.03$
Rovekamp-Abels et al,[19] range					
All	125	6 (5-8)	121	7 (5-10)	1 (−0.05 to 2.1)
Infants ≤ 1000g	55	8 (6-10)	56	8 (7-11)	0 (−1.5 to 1.5)
Infants ≥ 1000g	70	6 (5-7)	65	5.5 (5-8)	−0.5 (−1.6 to 0.6)
Schanler, et al,[21] SD					
All Prime 10d	43	29 ± 19	39	33 ± 19	$P = .001$
All NPO 10d	45	29 ± 9	44	29 ± 9	
Silvestre et al,[22] SD	40	12 ± 8	42	15 ± 10	NS

[a] *Toce et al,[23] NS data not reported as an outcome.*
[b] *Two hourly versus three hourly; outcome: days to full enteral feeding.*
[c] *Three hourly versus continuous; outcome: days to full enteral feeding.*

Gastric Residual Volumes

Five of 10 studies reported the frequency of checking gastric residuals[14,16,17,19,21]; however only 3 studies provided data on the volumes measured.[17,19,21] The only RCT that compared 2 and 3 hourly intervals measured gastric residuals before each feed in both intervention groups but did not provide data on volumes.[16] Feeding intolerance presenting with an increase in residuals and abdominal distention was higher, though not significantly in the 2 hourly intervention groups, 19% versus 13% in the 3 hourly groups. This had no impact on the duration to attain full feedings. The study by Dsilna et al[17] had 3 intervention groups: continuous nasogastric, 3 hourly intermittent nasogastric, and 3 hourly intermittent orogastric. Gastric residuals were checked every 6 hours in the 3 hourly interval groups and every 8 hours in infants fed continuously or more frequently if feeding intolerance was noted. The incidence of increased gastric residuals and vomiting was higher in the orogastric 3 hourly interval group than both the continuous and 3 hourly naso-gastric groups, although this was not deemed to be significant ($P = .055$ and .090, respectively). Gastric residual volumes were measured 8 hourly in both the continuous and 3 hourly interval groups in the most recent and largest RCT by Rovekamp-Abels et al.[19] Infants fed 3 hourly had lesser volumes of gastric residuals than those who were fed continuously, mean difference 0.9 mL/kg/d (95% CI, 0.1-1.7). In a subgroup analysis on infants weighing ≤1000 g, fewer residuals were also found among those fed 3 hourly than continuously, mean difference 2.1 mL/kg/d (95% CI, 0.9-3.3). Although the increased residuals resulted in more feeding interruptions, it did not ultimately impact on the duration to attain full feedings.[19] Schanler et al[21] assigned infants to 1 of 4 treatment combinations, comparing the presence or absence of gastrointestinal priming for 10 days plus continuous infusion of milk versus intermittent (3 hourly interval) feedings. They measured gastric residuals every 3 hours in all infants. Infants fed continuously had significantly more gastric residuals of greater than 50% of the 3-hour feeding volume than those fed at a 3 hourly intermittent interval (2.3 ± 2.9 vs 1.2 ± 1.8 $P < .001$).[21] Only 1 study reported a policy of replacing residuals.[14] No information was provided on whether residuals were discarded or returned in the remainder included studies.

Days on Parenteral Nutrition

Parenteral nutrition commences at birth and is discontinued once an infant is tolerating sufficient volumes of enteral feeds. Only 4 of the 10 studies reported on duration of parenteral nutrition.[15,16,20,21] In 1 study, the 3 hourly group was more likely than the 2 hourly group to have feeds withheld for over 1 week (OR = 4.7; 95% CI, 1.9-11.7) and were more likely to receive parenteral nutrition for a duration of 28 days (OR = 4.7; 95% CI, 1.5-14.4).[15] None of the other studies found a difference in the duration of parenteral nutrition.[16,20,21]

Secondary Outcomes

Growth

Time taken to regain birth weight was the most commonly measured outcome to assess growth in 7 of 10 studies.[14,16-19,21,22] While there were no observable differences in growth, only 1 of the selected studies reported weight gain being significantly slower in the continuous fed group versus the 3 hourly intermittent group ($P = .02$).[21] The average days to regain birth weight among the different studies varied from 8 to 18 days. One trial calculated growth by measuring leg length and found infants fed continuously had better outcomes.[17] Trials that assessed somatic growth by length, head circumference, and skinfold thickness found no differences between different feed intervals.[21-23]

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is an inflammatory bowel disease with or without necrosis.[29] VLBW infants are most at risk of developing NEC, the consequences for whom can be severe, including death, prolonged need for hospitalization, and assisted nutrition.[30] None of the trials was sufficiently large enough to detect a statistically significant difference in the incidence of NEC, and no differences were reported between the feeding intervals.

Mechanical Ventilation

Seven of 10 studies reported on ventilation, either on duration or numbers of infants who were ventilated at some stage of the study.[14,15,17-21] Two of the 3 studies that compared 2 and 3 hourly intervals reported on the duration of invasive ventilation.[15,20] Duration (days) intubated was no different between 2 and 3 hourly feeding intervals in the study by DeMauro et al.[15] The study by Rudiger et al[20] reported a significantly shorter duration of noninvasive ventilation in the 2 hourly versus 3 hourly groups ($P < .005$). The third selected study, which compared 2 and 3 hourly intervals, described the incidence of respiratory distress as being 56% in the 2 hourly intervention group and 73% in the 3 hourly group, but no data are provided on how this was measured.[16] Akintorin et al [14] reported feeding intolerance being associated with a longer duration of ventilation than those infants without feeding intolerance, yet no differences in the days spent on a ventilator were observed between either those fed continuously or 3 hourly. Rovekamp-Abels et al[19] compared days of invasive and noninvasive ventilation among those fed continuously or 3 hourly. The duration of ventilation was higher among infants in the study who weighed ≤1000 g. Their results suggest that the continuous feeding interval may be associated with a longer duration of both invasive and noninvasive ventilation than an intermittent 3 hourly interval.

DISCUSSION

Time to reach full enteral feeding is a good indicator of gastrointestinal tolerance and was a measured outcome in all but one of the included studies in this review. However, differences in how full feeds are defined varied across studies, compounded by the definition and management of feed intolerance made comparisons difficult. Initiation of feeds, the rate of advancement, choice of milk, and placement of the feeding tube contributed to the heterogeneity of the data. The average duration to achieve full feedings ranged from less than 10 and up to 34 days between different studies. Variations in the definition of full feedings limit the comparability of this outcome. Ideally, a standard definition of full feedings of 130 to 150 mL/kg/d tolerated for at least 48 hours should be used in future studies. The association with the feeding interval was more difficult to quantify, as some studies took over 3 weeks to establish full feeds in both interventions whereas others achieved the same outcome in less than 10 days regardless of the feeding interval. Conflicting results in favor of both 3 hourly or continuous intervals were reported. Although subject to the limitations of retrospective research in one of the larger studies in the review, the more positive outcomes seen with 2 hourly intervals versus 3 hourly intervals were demonstrated in all gestations and had the biggest effect among the most premature infants in their sample.[15] Given the small samples and the small number of studies, further research is needed to determine whether the benefits of 2 hourly intervals can be replicated in adequately powered RCTs.

Considerable variations in practice exist on the feeding interval and in how premature infants are fed.[8] A bolus feeding interval, such as 2 or 3 hourly, alternates periods of feeding and fasting, similar to how healthy term infants feed. Bolus feeds are physiologically natural, promoting the cyclical release of gastrointestinal tract hormones to stimulate gut maturation and motility.[31,32] A study on the effects of feeding interval on mesenteric blood flow velocity suggested that a 3 hourly interval initiates a more physiological postprandial response than hourly.[33] This effect was also influenced by the composition of milk, favoring human milk over formula. In contrast, continuous intervals avoid the larger feeding volumes and longer intervals, which may be potentially stressful to the extremely small preterm infant. Continuous milk feeds may interfere with lower esophageal sphincter return, encouraging development of gastrointestinal reflux.[34] The normal sensory priming of the cephalic phase is absent, and the physiological stomach filling and emptying are disturbed.[32,35] Disadvantages of continuous feeds delivered by infusion pumps may be the loss of nutrients and minerals in the delivery system, as fat adheres to the inner wall of the tubing.[36-38]

Disparities in the assessment of feeding intolerance by measuring residuals were seen across the included studies. Routine practice prior to giving a feed via an orogastric or naso-gastric tube is to aspirate the infant's stomach contents, to measure the volume and color of the gastric residual.[3,39] There is very little scientific evidence to support the utility of checking gastric residuals at all and the practice may result in delayed feeding without cause.[30] This was investigated in an RCT study including 60 VLBW infants. The authors found no benefit in routine gastric residual evaluation and demonstrated a shorter duration to full enteral feeds in those infants who did not undergo this intervention routinely.[39] Infants fed at a 2 hourly interval, who potentially may have prefeed residuals checked routinely, are at risk of having their gastric contents aspirated up to 12 times daily. Hence, the importance of standardized feeding regimens to assess and manage perceived feeding intolerance. Limited data provided in relationship to gastric residual volumes in this review (3 of 10 studies) made it difficult to interpret the relationship of gastric residual volumes with the feeding interval. Yet, smaller infants took longer to achieve full feedings due to increased residual volumes and overall there was a trend toward increased residuals among infants fed continuously rather than with a bolus interval.

Days on parenteral nutrition has been suggested as a surrogate marker of feeding intolerance.[40] Comorbidities, central line access, and peripheral access influence this outcome, so in isolation it is not necessarily a reliable marker. No correlation with NEC and feeding intervals was identified in this review; however, none of the trials was large enough to detect a significant difference.

Noninvasive ventilation may cause abdominal distension, a feature often associated with feed intolerance.[2] Nasal continuous positive airway pressure (nCPAP) decreases pre- and postprandial intestinal blood flow in preterm infants.[41] The significant difference ($P < .005$) in duration of nCPAP observed in the 2 hourly versus 3 hourly retrospective study warrants further investigation.[20] The authors speculated that the lower volume of the 2 hourly intervals does not alter lung mechanics as much as the higher volume administered every 3 hours. If that is the case, then it is arguable that the same outcome would be apparent in favor of continuous versus 3 hourly feeds, but this has not been demonstrated. A second benefit of 2 hourly feeding was seen in the shorter duration of

Summary of Recommendations	
What we know:	• There is not a widely recognized consensus on the optimal feeding interval in low birth-weight premature infants. • The timely establishment of enteral feeds is imperative to avoiding complications associated with venous access and the adverse effects of parenteral nutrition. • The duration to achieve full enteral feeding increases with a lower gestational age.
What still needs to be studied:	• Can we reduce feeding interruptions by changing the feeding interval? • How often should gastric residuals be evaluated and should residuals be refed?
What can we do today:	• When using the term intermittent, clarify whether you mean hourly, 2 hourly, or 3 hourly. • Standardized feeding regimens, incorporating a rational approach to feed intolerance and management, are key to achieving optimal nutrition. • Tolerating enteral feedings of 130 to 150 mL/kg/d for at least 48 hours should be agreed as a standard definition of "full enteral feedings."

phototherapy treatment.[20] It is possible that the more frequent 2 hourly intervals stimulate gut motility, thereby increasing fecal bilirubin clearance. Stooling patterns have not been described in detail in these studies, so no conclusion can be made on this outcome. Bolus feeds delivered by gravity provide opportunities for parental involvement in their infant's care. In the author's experience, parents often develop a pattern, timing visits around their infant's feedings. Delivering the feed gives an added purpose and pleasure to the visit. Continuous feeds are usually administered via an infusion pump, which may involve considerable cost to purchase and maintain. Intermittent bolus feeds require less equipment to administer than feeds administered by the electric pump.

Limitations of This Review

Very little research on infant feeding intervals exists; hence, this review was not limited to just RCTs. Due to the paucity of research in VLBW infants (birth weight ≤1500 g), an upper weight limit of ≤1750 g was used. Significant heterogeneity existed in how feeding outcomes were measured and presented, making comparisons of the data very difficult. Furthermore, adequately powered RCTs are needed, especially in infants with birth weights ≤1500 g in whom the incidence of feeding intolerance is likely to be greater.

CONCLUSION

The results of this review are not definitive, although it does serve to highlight the limited clinical evidence available to determine an optimal feeding interval. Recent approaches to feeding premature infants have recognized the value of using human milk and the use of standardized feeding regimens.[1] Although the data examined provided conflicting results, it would seem to favor bolus intermittent feeding intervals over continuous. While this review found a trend toward increased residuals and feed interruptions in continuously fed infants, this did not always impact on duration to full feeds. A 2 hourly interval in VLBW infants appears to shorten the duration to full feeding and possibly the duration of noninvasive ventilator support when compared with a 3 hourly interval. If feeding tolerance is related to volumes of milk, the smaller volume of the 2 hourly interval is more likely to be better tolerated than a 3 hourly volume, although this outcome has not yet been demonstrated in an adequately powered RCT. Gastric residuals were lower in the 3 hourly intermittent bolus groups than in the continuous feeding groups. No differences in the time to regain birth weight were observed among any of the feeding intervals. Intermittent feeds are potentially more cost-effective to administer, as less equipment is required than for continuous feeds. More research studies are needed to provide evidence on optimal feeding intervals for premature and VLBW infants. Finally, a distinction should be made between 2 and 3 hourly intervals when discussing intermittent bolus feeds.

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