ORIGINAL ARTICLE

Controlled Trial of Two Incremental Milk-Feeding Rates in Preterm Infants

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ABSTRACT

BACKGROUND

Observational data have shown that slow advancement of enteral feeding volumes in preterm infants is associated with a reduced risk of necrotizing enterocolitis but an increased risk of late-onset sepsis. However, data from randomized trials are limited.

METHODS

We randomly assigned very preterm or very-low-birth-weight infants to daily milk increments of 30 ml per kilogram of body weight (faster increment) or 18 ml per kilogram (slower increment) until reaching full feeding volumes. The primary outcome was survival without moderate or severe neurodevelopmental disability at 24 months. Secondary outcomes included components of the primary outcome, confirmed or suspected late-onset sepsis, necrotizing enterocolitis, and cerebral palsy.

RESULTS

Among 2804 infants who underwent randomization, the primary outcome could be assessed in 1224 (87.4%) assigned to the faster increment and 1246 (88.7%) assigned to the slower increment. Survival without moderate or severe neurodevelopmental disability at 24 months occurred in 802 of 1224 infants (65.5%) assigned to the faster increment and 848 of 1246 (68.1%) assigned to the slower increment (adjusted risk ratio, 0.96; 95% confidence interval [CI], 0.92 to 1.01; P=0.16). Late-onset sepsis occurred in 414 of 1389 infants (29.8%) in the faster-increment group and 434 of 1397 (31.1%) in the slower-increment group (adjusted risk ratio, 0.96; 95% CI, 0.86 to 1.07). Necrotizing enterocolitis occurred in 70 of 1394 infants (5.0%) in the faster-increment group and 78 of 1399 (5.6%) in the slower-increment group (adjusted risk ratio, 0.88; 95% CI, 0.68 to 1.16).

CONCLUSIONS

There was no significant difference in survival without moderate or severe neurodevelopmental disability at 24 months in very preterm or very-low-birth-weight infants with a strategy of advancing milk feeding volumes in daily increments of 30 ml per kilogram as compared with 18 ml per kilogram. (Funded by the Health Technology Assessment Programme of the National Institute for Health Research; SIFT Current Controlled Trials number, ISRCTN76463425.)

Infants who are very preterm (<32 weeks of gestation) or who have a very low birth weight (<1500 g) are fed increasing volumes of milk per day until they reach full enteral feeding volumes. The approach to increasing the feeding volume per day is uncertain because of competing concerns. Observational studies have shown a higher risk of necrotizing enterocolitis[1-3] with rapid advancement of feeding volumes but are subject to bias; one was an uncontrolled study before and after the introduction of a slowly progressive tube-feeding schedule,[1] and two were small case–control studies.[2,3] Slower advances in feeding volume might, however, increase the risk of late-onset sepsis from longer exposure to parenteral feeding, as shown in a meta-analysis that also revealed no increase in necrotizing enterocolitis.[4] These conditions are both major causes of death and illness, including adverse neurodevelopmental outcomes.[5-8]

Existing trial data are insufficient to determine whether advancing enteral feeding volumes slowly (typically by <24 ml per kilogram of body weight per day) as compared with more quickly (by 30 to 40 ml per kilogram per day) affects outcomes of very preterm or very-low-birth-weight infants.[4,9-16] The Speed of Increasing Milk Feeds Trial (SIFT) therefore compared faster (30 ml per kilogram) with slower (18 ml per kilogram) daily increments in milk feeding volumes.

Methods

Trial Design and Procedures

The trial was a multicenter, parallel-group, randomized, controlled trial that followed a published protocol,[17] also available with the full text of this article at NEJM.org. The trial was approved by the East Midlands National Research Ethics Committee and the National Maternity Hospital Ethics Committee in Dublin and overseen by independent steering and data and safety monitoring committees.

Trial Participants

After written informed consent was obtained from parents, infants receiving less than 30 ml of milk per kilogram per day at randomization were eligible to participate if they were born before 32 weeks of gestation, had a birth weight of less than 1500 g, or both. Infants who had a known severe congenital anomaly or no realistic chance of survival or who were unlikely to be traceable for follow-up were ineligible.

Enrollment and Treatment

When clinicians were ready to start advancing feeding volumes, infants were randomly assigned to receive daily increments in feeding volume of 30 ml per kilogram (faster increment) or 18 ml per kilogram (slower increment). Computerized randomization was performed through a secure website hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit, University of Oxford. A minimization algorithm balanced prognostic factors: hospital, multiple birth, gestational age range (Table 1), and whether the birth weight was below the 10th percentile for gestational age. Infants from multiple births were assigned to the same treatment. All other aspects of feeding and care followed routine clinical practice in the individual units, including the capacity to stop or alter the rate of increase in feeding volume if clinically indicated. Data were collected at trial entry, including whether the infant had absent or reversed end-diastolic umbilical arterial blood flow identified on any antenatal ultrasonographic scan.

Primary and Secondary Outcomes

The primary outcome was survival without moderate or severe neurodevelopmental disability at 24 months of age, corrected for gestational age at birth. Moderate or severe neurodevelopmental disability was defined as any of the following: moderate or severe visual impairment (reduced vision uncorrected with aids, blindness in one eye with good vision in the contralateral eye, or blindness or light perception only), moderate or severe hearing impairment (hearing loss corrected with aids, some hearing loss uncorrected by aids, or deafness), moderate or severe gross motor impairment (inability to walk or sit independently), or moderate or severe cognitive impairment as assessed with the use of the Parent Report of Children's Abilities–Revised (PARCA-R) or clinical data if PARCA-R scores were missing. Total PARCA-R scores of less than 44 (range, 0 to 158, with lower scores indicating greater impairment) were used to identify children with moderate or severe developmental impairment.[18]

Secondary outcomes included death, death before discharge home, microbiologically confirmed or clinically suspected late-onset sepsis from trial

Table 1. Infant and Maternal Characteristics at Trial Entry.*

Characteristic	Faster Increment: 30 ml/kg/day (N=1394)	Slower Increment: 18 ml/kg/day (N=1399)
Male sex — no./total no. (%)	739/1394 (53.0)	726/1398 (51.9)
Infant's median age at randomization (IQR) — days	4 (3–6)	4 (3–6)
Birth weight <10th percentile for gestational age — no./total no. (%)	295/1394 (21.2)	291/1398 (20.8)
Gestational age at delivery		
Median (IQR) — wk	29 (27–30)	29 (27–30)
Distribution — no. (%)		
23 wk 0 days to 25 wk 6 days	205 (14.7)	201 (14.4)
26 wk 0 days to 27 wk 6 days	291 (20.9)	297 (21.2)
28 wk 0 days to 29 wk 6 days	377 (27.0)	383 (27.4)
30 wk 0 days to 31 wk 6 days	432 (31.0)	432 (30.9)
32 wk 0 days to 36 wk 6 days	88 (6.3)	86 (6.1)
≥37 wk 0 days	1 (0.1)	0
Birth weight		
Mean — g	1144.2±339.3	1142.3±328.9
Distribution — no. (%)		
<500 g	10 (0.7)	7 (0.5)
≥500 to <1000 g	494 (35.4)	509 (36.4)
≥1000 to <1500 g	661 (47.4)	677 (48.4)
≥1500 g	229 (16.4)	206 (14.7)
Infant heart rate >100 beats/min at 5 min — no./total no. (%)	1263/1374 (91.9)	1265/1381 (91.6)
Infant mean worst base excess within 24 hr after birth	–6.1±4.0	–6.1±3.9
Infant ventilated through endotracheal tube at randomization — no./total no. (%)	316/1392 (22.7)	293/1397 (21.0)
Infant had absent or reversed end-diastolic umbilical flow — no./total no. (%)	209/1372 (15.2)	226/1380 (16.4)
Median time from trial entry to first feed (IQR) — days	0 (0–0)	0 (0–1)
Mother's mean age at randomization — yr	30.5±6.2	30.7±6.2
Multiple pregnancy		
Any — no. (%)†	412 (29.6)	411 (29.4)
Singles‡	3	5
Twins§	358	359
Triplets¶	51	47
Cesarean section delivery — no./total no. (%)	841/1393 (60.4)	847/1399 (60.5)
Membranes ruptured >24 hr before delivery — no./total no. (%)	323/1377 (23.5)	338/1380 (24.5)

* Plus–minus values are means ±SD. Unless otherwise stated, the table gives the percentages of infants with data in that group of the trial who had (or whose mother had) the stated characteristic. The number of infants with missing data was as follows: for infant worst base excess within 24 hours after birth, 29 in the faster-increment group and 26 in the slower-increment group; for time from trial entry to first feed, 5 and 4, respectively; and for mother's age at randomization, 0 and 1. Percentages may not total 100 because of rounding. IQR denotes interquartile range. More details on gestational age, birth weight, and other characteristics are provided in Table S7.

† Sometimes, only one infant from a multiple pregnancy met the inclusion criteria and was recruited.

‡ Shown is the number of infants from multiple pregnancies in which the other fetuses were aborted, miscarried, or stillborn.

§ Shown is the number of infants who were one of twins.

¶ Shown is the number of infants who were one of triplets.

entry to discharge home, Bell's stage 2 or 3 necrotizing enterocolitis (stages range from 1 to 3, with higher stages indicating greater severity of disease) from trial entry to discharge home, time taken to reach full milk feeding volumes (150 ml per kilogram per day for 3 consecutive days), growth (change in weight and head circumference z score for gestational age) from birth to discharge home, duration of parenteral feeding, duration of time in intensive care, duration of hospital stay to discharge home, diagnosis of cerebral palsy by a doctor or other health professional, moderate or severe neurodevelopmental disability at 24 months (corrected for gestational age), and the individual components of the definition of moderate or severe neurodevelopmental disability.

Classifications of moderate or severe neurodevelopmental disability, late-onset sepsis, and necrotizing enterocolitis were confirmed by an end-point review committee whose members were unaware of the trial-group assignments; the committee used standard definitions if outcomes were ambiguous or data were missing (see the Supplementary Appendix, available at NEJM.org). All data-collection forms were assessed independently by pairs of clinicians who were unaware of the trial-group assignments. Owing to rounding of the feeding rate to the nearest 0.5 ml per kilogram or small changes in daily weight in the clinical setting, some infants receiving "full enteral feeding volumes" received only 145 to 149 ml per kilogram per day. We therefore considered an infant to be receiving full enteral feeding volumes if at least 145 ml per kilogram per day was administered for 3 consecutive days. Cases that did not meet these criteria were reviewed by the end-point review committee to determine whether a sustained level of feeding below this had been achieved. Examples of this included feeds being stopped during transfer or a procedure and use of higher-calorie formula.

STATISTICAL ANALYSIS

We estimated that 80% of infants would survive to 2 years and that 11% of survivors would have moderate or severe neurodevelopmental disability.[19] We anticipated that the primary outcome would occur in 71% of the comparator (slower-increment) group. With a total sample size of 2500 and allowance for a questionnaire response rate of 80%, there would be 90% power to detect an absolute difference of 6.3 percentage points in the incidence of the primary outcome between the trial groups with a two-sided significance level of 5%. Similarly, enrollment of 2500 infants would provide the trial with 90% power to detect an absolute difference of 5.4 percentage points (from 25.0% in the comparator group) in the incidence of late-onset sepsis[20] and an absolute difference of 3.5 percentage points (from 6.0% in the comparator group) in the incidence of necrotizing enterocolitis (Bell's stage 2 or 3).[21-23]

Subsequently, an inflation factor of 1.12 was applied to the sample size to allow for multiple births, since infants from a multiple birth received the same treatment and we anticipated correlated outcomes. This adjustment assumed the percentage of multiple births to be 25% and an intraclass correlation coefficient of 0.9 for the primary outcome at 24 months, corrected for gestational age.[24] The total target sample size was therefore increased to 2800.

Demographic factors, clinical characteristics, and outcomes were summarized with counts and percentages for categorical variables, means and standard deviations for normally distributed continuous variables, and medians and interquartile or simple ranges for other continuous variables. Outcomes were analyzed on an intention-to-treat basis with the use of the slower-increment group as the comparator.

Risk ratios and 95% confidence intervals were calculated for the primary outcome at 24 months (corrected for gestational age) and for the discharge outcomes of late-onset sepsis and necrotizing enterocolitis. We used 99% confidence intervals for all other dichotomous outcomes, to take account of the number of hypothesis tests performed, without full adjustment for multiple testing. For normally distributed continuous outcomes, the mean difference and 99% confidence interval are presented; for skewed continuous variables, the median difference and 99% confidence interval are presented. Adjusted risk ratios were estimated with the use of log-binomial regression, or log-Poisson regression with a robust variance estimator if the binomial model failed to converge. Linear regression was used for normally distributed continuous variables, and quantile regression was used for skewed continuous variables. The primary inference was based on the analysis with adjustment for the minimization factors at randomization. Center was fitted as a

random effect, and the other minimization factors were fitted as fixed effects. A unique identifier for each mother was nested within center to take account of the additional level of clustering due to multiple births and siblings. This method facilitates the calculation of robust standard errors to allow for the lack of independence in trial-group assignments and the potential correlation in outcome.

The consistency of the effects of advancing milk feeding volumes on the incidence of the primary outcome, late-onset sepsis, and necrotizing enterocolitis across specific subgroups was assessed with the use of the statistical test of interaction. Prespecified subgroup analyses included week of gestation at birth, birth weight (<10th percentile for gestational age vs. ≥10th percentile), and type of milk received during the hospital stay (breast milk only vs. formula only vs. both breast milk and formula). Post hoc analysis assessed the effect of the increments on late-onset sepsis and necrotizing enterocolitis in infants with absent or reversed end-diastolic umbilical flow on antenatal Doppler ultrasonography. Other deviations from the protocol include the use of quantile regression instead of Cox regression to analyze the time to full feeding volumes (because the Cox proportional-hazards assumption was not satisfied) and mixed-effect log-binomial or log-Poisson models instead of generalized estimating equations (owing to the ease and flexibility of these methods, which were not in common use when the trial was conceived). We performed a sensitivity analysis to examine the effect of missing data at 24 months on the primary outcome, by considering different scenarios that departed from the assumption that data were missing completely at random.

RESULTS

PARTICIPANTS

A total of 2804 infants were recruited between June 8, 2013, and June 30, 2015, from 55 hospitals. Infant and maternal characteristics were similar in the two trial groups (Table 1, and Table S3A through S3C in the Supplementary Appendix). All infants received the assigned intervention, but 69 discontinued the intervention, 66 owing to clinician or parental preference and 3 owing to transfer to a nonparticipating hospital (Fig. 1). For 11 infants, parental consent was withdrawn, and their data were not available for analysis. The remainder were included in modified intention-to-treat analyses. Outcome data at discharge home were not available for 8 infants; their data were included in the analyses, except when knowledge of discharge or the date of discharge was required. A total of 68 infants in the faster-increment group and 77 in the slower-increment group died before 24 months, corrected for gestational age (Table 2). Assessment of the primary outcome at 24 months, corrected for gestational age, was possible in 1224 infants (87.4%) in the faster-increment group and 1246 (88.7%) in the slower-increment group (Fig. 1).

PRIMARY AND SECONDARY OUTCOMES AT 24 MONTHS OF AGE, CORRECTED FOR PREMATURITY

At 24 months (corrected for gestational age), death had occurred in 68 of 1224 infants (5.6%) in the faster-increment group and in 77 of 1246 (6.2%) in the slower-increment group, and moderate or severe neurodevelopmental disability had occurred in 354 infants in the faster-increment group and in 321 in the slower-increment group (Table 2). There was no significant difference between infants receiving a faster daily increment (30 ml per kilogram) and those receiving a slower daily increment (18 ml per kilogram) regarding the primary outcome of survival without moderate or severe neurodevelopmental disability at 24 months, corrected for gestational age (Table 2). There were also no significant differences between the faster-increment group and the slower-increment group regarding the individual components of the composite outcome. The results were similar in sensitivity analyses of missing data that used different approaches to impute missing data (Table S5B).

SECONDARY OUTCOMES

The faster-increment group reached full milk feeding volumes at a median of 7 days, as compared with 10 days in the slower-increment group (adjusted median difference, –2.7 days; 99% confidence interval [CI], –3.1 to –2.4); the duration of parenteral nutrition from trial entry to discharge home was 9 days and 11 days, respectively (adjusted median difference, –2.2 days; 99% CI, –2.7 to –1.6) (Table 3). There was no evidence of significant between-group differences regarding confirmed or clinically suspected late-onset sepsis, Bell's stage 2 or 3 necrotizing enterocolitis, death

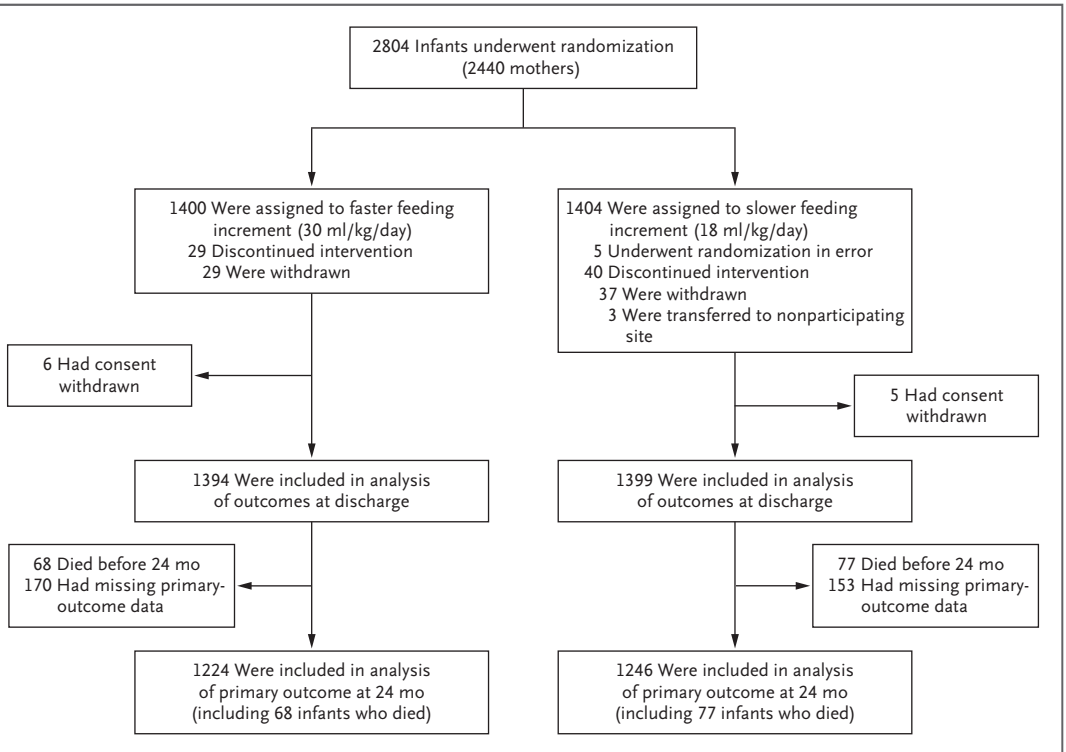

Figure 1. Randomization, Intervention, and Analysis.

during hospitalization, weight and head circumference standard-deviation scores at discharge, duration of time in intensive care, and duration of hospital stay from trial entry (Table 3).

After adjustment for minimization factors, moderate or severe motor impairment occurred in 7.5% of the infants in the faster-increment group and 5.0% of those in the slower-increment group (adjusted risk ratio, 1.48; 99% CI, 1.02 to 2.14) (Table 2). There was no evidence of significant between-group differences for the other three components of the disability definition.

SUBGROUP ANALYSES

There was weak evidence of statistical interaction between the type of milk (breast milk only, formula only, or both breast milk and formula) and feeding increment with respect to survival without moderate or severe neurodevelopmental disability at 24 months, corrected for gestational age (P=0.045). For infants fed with formula only, survival without moderate or severe neurodevelopmental disability was seen in 12 of 30 infants (40%) in the faster-increment group, as compared with 28 of 40 (70%) in the slower-increment group (Fig. 2 and Table S5C). There was no evidence of differential treatment effects for any other prespecified subgroup from trial entry until discharge or at 24 months, corrected for gestational age (Fig. 2 and Figs. S2 and S3). Post hoc analysis did not show an interaction between antenatal absent or reversed end-diastolic umbilical flow and faster or slower feeding increments (Tables S1 and S2).

SERIOUS ADVERSE EVENTS

Four serious adverse events that were not prespecified as outcomes were reported. One infant in each group had an intracardiac thrombus, with one of these extending into the superior vena cava and causing renal failure and death (faster-increment group). One infant (in the faster-increment group) had conjugated hyperbilirubinemia, which resolved, and one infant (in the slower-increment group) became dehydrated briefly with extravasation from a central venous catheter.

DISCUSSION

In this large, pragmatic, randomized, controlled trial involving infants with a gestational age of less

Table 2. Primary and Secondary Outcomes at 24 Months of Age, Corrected for Gestational Age.*

Outcome	Faster Increment: 30 ml/kg/day (N=1394)	Slower Increment: 18 ml/kg/day (N=1399)	Unadjusted Effect Measure (CI)†	Adjusted Effect Measure (CI)†‡
Primary outcome				
Survival without moderate or severe neurodevelopmental disability — no./total no. (%)§¶	802/1224 (65.5)	848/1246 (68.1)	0.96 (0.91 to 1.02)	0.96 (0.92 to 1.01)
Survival — no. (%)	1326 (95.1)	1322 (94.5)	1.01 (0.99 to 1.02)	1.01 (0.99 to 1.03)
Moderate or severe neurodevelopmental disability — no./total no. (%)	354/1156 (30.6)	321/1169 (27.5)	1.12 (0.98 to 1.28)	1.10 (0.97 to 1.25)
Secondary outcomes				
Moderate or severe visual impairment — no./total no. (%)	21/1156 (1.8)	16/1171 (1.4)	1.33 (0.57 to 3.10)	1.28 (0.43 to 3.83)
Moderate or severe hearing impairment — no./total no. (%)	58/1143 (5.1)	41/1172 (3.5)	1.45 (0.86 to 2.46)	1.43 (0.79 to 2.57)
Moderate or severe motor impairment — no./total no. (%)	87/1164 (7.5)	59/1177 (5.0)	1.49 (0.96 to 2.32)	1.48 (1.02 to 2.14)
Moderate or severe cognitive impairment — no./total no. (%)	307/1156 (26.6)	289/1170 (24.7)	1.08 (0.89 to 1.30)	1.06 (0.89 to 1.27)
PARCA-R‖				
Mean composite score	72.5±38.3	73.9±37.8	−1.5 (−6.3 to 3.4)	−0.6 (−4.8 to 3.6)
Mean score on Nonverbal Cognition Scale	25.1±6.2	25.5±5.7	−0.5 (−1.2 to 0.3)	−0.4 (−1.0 to 0.3)
Mean score on Vocabulary Subscale	39.3±29.7	40.3±30.1	−1.0 (−4.8 to 2.8)	−0.4 (−3.7 to 3.0)
Mean score on Sentence Complexity Subscale	7.9±5.7	7.9±5.4	−0.1 (−0.8 to 0.6)	−0.1 (−0.7 to 0.6)
Diagnosis of cerebral palsy by a doctor or other health professional — no./total no. (%)	58/1084 (5.4)	35/1099 (3.2)	1.68 (0.97 to 2.91)	1.66 (0.97 to 2.84)

* Plus–minus values are means ±SD. CI denotes confidence interval.

† Risk ratios are shown for binary outcomes, and mean differences are shown for continuous outcomes. Shown are 95% confidence intervals for survival without moderate or severe neurodevelopmental disability, survival, and moderate or severe neurodevelopmental disability and 99% confidence intervals for all other outcomes. The 99% confidence intervals have not been fully adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

‡ According to a prespecified plan, the effect measure was adjusted for minimization factors — collaborating hospital, single or multiple birth, gestational age at birth, and whether the birth weight was below the 10th percentile for gestational age — when technically possible.

§ P=0.16 for testing whether adjusted risk ratio is equal to 1.

¶ Moderate or severe neurodevelopmental disability was defined as one or more of the following: moderate or severe visual impairment, moderate or severe hearing impairment, moderate or severe motor impairment, or moderate or severe cognitive impairment. Moderate or severe visual, hearing, and motor impairments were defined according to the British Association of Perinatal Medicine.[25] Moderate or severe cognitive impairment was defined by a composite score on the Parent Report of Children's Abilities–Revised (PARCA-R) of less than 44 (range, 0 to 158, with lower scores indicating greater impairment).

‖ Scores on the Nonverbal Cognition Scale range from 0 to 34, scores on the Vocabulary Subscale range from 0 to 100, and scores on the Sentence Complexity Subscale range from 0 to 24; on all scales, lower scores indicate greater impairment. The number of infants with missing data was as follows: for composite score, 419 in the faster-increment group and 392 in the slower-increment group; for score on the Nonverbal Cognition Scale, 414 and 390, respectively; for score on the Vocabulary Subscale, 412 and 383; and for score on the Sentence Complexity Subscale, 405 and 379.

than 32 weeks or a birth weight of less than 1500 g, advancing milk feeding volumes at daily increments of 30 ml per kilogram as compared with 18 ml per kilogram did not affect survival without moderate or severe neurodevelopmental disability at 24 months, corrected for gestational age. The speed of increment in feeding volumes also did not affect the risks of late-onset sepsis, necrotizing enterocolitis, or death during hospitalization.

Secondary-outcome analysis suggested that the number of days to reach full milk feeding volumes and the number of days of parenteral nutrition were lower with faster increments than with slower increments. Although these feeding outcomes seem to favor faster increments, the risk of moderate or severe motor impairment was unexpectedly higher in the faster-increment group than in the slower-increment group. This obser-

Table 3. Outcomes at Discharge to Home.*

Outcome	Faster Increment: 30 ml/kg/day (N=1394)	Slower Increment: 18 ml/kg/day (N=1399)	Unadjusted Effect Measure (CI)†	Adjusted Effect Measure (CI)†‡
Key discharge outcomes				
Microbiologically confirmed or clinically suspected late-onset sepsis — no./total no. (%)	414/1389 (29.8)	434/1397 (31.1)	0.96 (0.85 to 1.08)	0.96 (0.86 to 1.07)
Necrotizing enterocolitis, Bell's stage 2 or 3 — no. (%)	70 (5.0)	78 (5.6)	0.90 (0.66 to 1.24)	0.88 (0.68 to 1.16)
Secondary outcomes				
Death before discharge — no./total no. (%)	60/1392 (4.3)	65/1393 (4.7)	0.92 (0.59 to 1.45)	0.91 (0.55 to 1.53)
Median time to reach full milk feeding volumes (IQR) — days	7 (7 to 10)	10 (9 to 13)	−3.0 (−3.3 to −2.7)	−2.7 (−3.1 to −2.4)
Mean weight standard-deviation score at discharge home§	−1.5±1.1	−1.5±1.1	−0.04 (−0.15 to 0.08)	−0.02 (−0.11 to 0.08)
Mean head circumference standard-deviation score at discharge home§	−0.8±1.5	−0.7±1.7	−0.09 (−0.27 to 0.09)	−0.07 (−0.24 to 0.10)
Median duration of parenteral feeding from trial entry to discharge home (IQR) — days	9 (7 to 14)	11 (9 to 16)	−2.0 (−2.4 to −1.6)	−2.2 (−2.7 to −1.6)
Median length of time in intensive care from trial entry to discharge home (IQR) — days	7 (4 to 21)	8 (4 to 21)	−1.0 (−2.6 to 0.6)	−0.4 (−1.5 to 0.6)
Median length of hospital stay from trial entry to discharge home (IQR) — days¶	54 (37 to 81)	55 (38 to 78)	−1.0 (−5.2 to 3.2)	0.1 (−1.9 to 2.0)

* Plus–minus values are means ±SD. The number of infants with missing data was as follows: for time to reach full milk feeding volumes (145 ml per kilogram per day for 3 consecutive days), 72 in the faster-increment group and 102 in the slower-increment group; for weight standard-deviation score at discharge home, 75 and 77, respectively; for head circumference standard-deviation score at discharge home, 258 and 228; for duration of parenteral feeding from trial entry to discharge home, 10 and 21; for length of time in intensive care from trial entry to discharge home, 71 and 87; and for length of hospital stay from trial entry to discharge home, 62 and 71.

† Risk ratios are shown for binary outcomes, and median or mean differences are shown for continuous outcomes. Shown are 95% confidence intervals for late-onset sepsis and necrotizing enterocolitis (Bell's stage 2 or 3; stages range from 1 to 3, with higher stages indicating greater severity of disease) and 99% confidence intervals for all other outcomes. The 99% confidence intervals have not been fully adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

‡ According to a prespecified plan, the effect measure was adjusted for minimization factors — collaborating hospital, single or multiple birth, gestational age at birth, and whether the birth weight was below the 10th percentile for gestational age — when technically possible.

§ Scores were calculated with the use of the British 1990 growth reference (revised September 2009). The standard-deviation scores indicate how far an infant is from the population mean weight and head circumference for infants of the same age and sex. For example, infants with a standard-deviation score of −2 or less compare approximately with the bottom 2% of the reference population.

¶ The analysis included data from surviving infants only.

vation is unexplained, and there were not more cases of late-onset sepsis or necrotizing enterocolitis in the faster-increment group. It is possible that it is a chance finding, since it was one of multiple secondary outcomes assessed, but biologically plausible explanations include increased cardiorespiratory events from pressure on the diaphragm or inability to absorb enteral nutrition.

The trial was pragmatic, and, apart from daily increments in milk volume, clinician preference and unit guidelines determined other care. The primary outcome could be assessed in 87.4% of the infants in the faster-increment group and in 88.7% of those in the slower-increment group at 24 months, corrected for gestational age. Similar results were obtained from sensitivity analyses with imputation of missing data.

As compared with previous trials,[9-16] the present trial included larger numbers of high-risk infants, including 1020 extremely low-birth-weight infants (<1000 g), 994 extremely preterm infants (<28 weeks of gestation), and 435 infants with absent or reversed end-diastolic umbilical flow on antenatal Doppler studies. Subgroup analyses of higher-risk infants were reassuring, because there was no suggestion of worse outcomes with faster increments than with slower increments. Infants were a median of 4 days old at commencement of the intervention, and therefore the trial does not inform the relative safety of these feed-

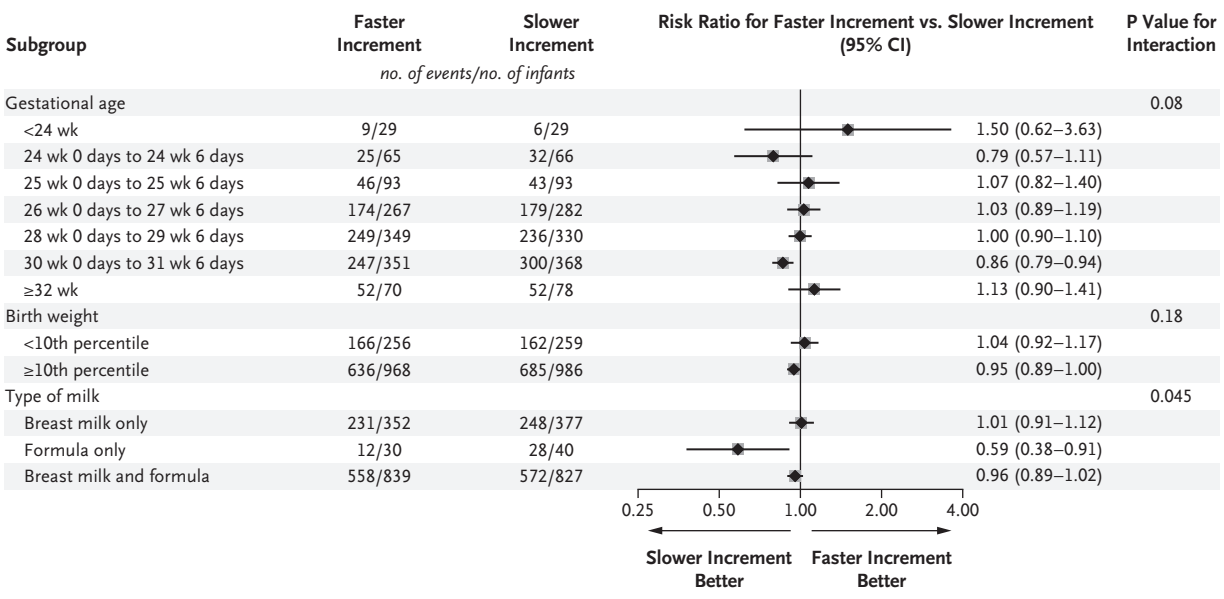

Figure 2. Subgroup Analyses for the Primary Outcome.

The primary outcome was survival without moderate or severe neurodevelopmental disability at 24 months of age, corrected for gestational age. P values for interaction were adjusted for minimization factors — collaborating hospital, single or multiple birth, gestational age at birth, and whether the birth weight was below the 10th percentile for gestational age — when technically possible. P values and confidence intervals were not adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

ing volume increments in the first few days after birth. Further study would be needed to address enteral feeding in these infants, other speeds of advancing feeding volumes, and different milks. Infants born at extremely early gestational ages or with an extremely low birth weight may react differently than other infants to the speed of increasing feeding volumes. We did not find appreciable differences in outcome according to these variables, but our trial included relatively small numbers of infants in these categories, and further research may be warranted in these groups.

Observational data have suggested a reduced risk of necrotizing enterocolitis among very preterm or very-low-birth-weight infants fed breast milk.[26] Most participating infants in SIFT were fed, at least partially, with breast milk. Only 2.8% of the infants who were followed to 24 months were fed formula alone, with similar numbers in the two groups. With respect to these formula-only infants, the finding of a poorer outcome in the faster-increment group than in the slower-increment group probably represents a chance finding, given the small numbers of infants, substantial loss to follow-up, and multiple comparisons performed without adjustment for multiple testing. The risk–benefit balance of enteral-feeding strategies may differ between human milk–fed infants and formula-fed infants.

The trial was unblinded, because it was considered impractical for caregivers and parents to be unaware of the trial-group assignments. This is unlikely to have influenced the ascertainment of the most important outcomes, which were reviewed by end-point review committees whose members were unaware of the trial-group assignments. Although it is possible that knowledge of the trial-group assignments could alter clinician practice (e.g., preferentially stopping feeds given at faster rather than slower increments in cases of suspected necrotizing enterocolitis), this is unlikely to have substantively affected the results.

In conclusion, the speed of advancing enteral feeding volumes — daily increments of 30 ml per kilogram as compared with 18 ml per kilogram — did not have a significant effect on the primary outcome of survival without moderate or severe neurodevelopmental disability, nor did

it affect the risks of late-onset sepsis or necrotizing enterocolitis in very preterm or very-low-birthweight infants.

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