

ORIGINAL ARTICLE

Early enteral feeding and nosocomial sepsis in very low birthweight infants

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Background: The interrelations between early enteral feeding, necrotising enterocolitis (NEC), and nosocomial sepsis (NS) remain unclear.

Objective: To evaluate the effect of age at the introduction of enteral feeding on the incidence of NS and NEC in very low birthweight (VLBW < 1500 g) infants.

Methods: Data were collected on the pattern of enteral feeding and perinatal and neonatal morbidity on all VLBW infants born in one centre during 1995–2001. Enteral feeding was compared between infants with and without NS and/or NEC.

Results: The study sample included 385 infants. Of these, 163 (42%) developed NS and 35 (9%) developed NEC. Enteral feeding was started at a significantly earlier mean (SD) age in infants who did not develop nosocomial sepsis (2.8 (2.6) v 4.8 (3.7) days, $p = 0.0001$). Enteral feeding was introduced at the same age in babies who did or did not develop NEC (3.1 (2) v 3.7 (3) days, $p = 0.28$). Over the study period, the mean annual age at the start of enteral feeding fell consistently, and this correlated with the mean annual incidence of NS ($r^2 = 0.891$, $p = 0.007$). Multiple logistic regression analysis showed age at start of enteral feeding, respiratory distress syndrome, and birth weight to be the most significant predictors of risk of NS ($p = 0.0005$, $p = 0.024$, $p = 0.011$).

Conclusions: Early enteral feeding was associated with a reduced risk of NS but no change in the risk of NEC in VLBW infants. These findings support the use of early enteral feeding in this high risk population, but this needs to be confirmed in a large randomised controlled trial.

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Early introduction of enteral feeding in preterm infants is associated with improved growth, better nitrogen balance, and maintenance of the intestinal barrier.^{1–3} However, early feeding has been implicated in the pathogenesis of necrotising enterocolitis (NEC) and, accordingly, initiation of enteral feeding is often delayed for several days to weeks.^{4–5}

The incidence of NEC in very low birthweight (VLBW) infants is 5–12%, and up to 30% will have at least one episode of nosocomial sepsis during their stay in the neonatal intensive care unit (NICU).^{6–7}

In studies of adults after injury, prospective randomised controlled trials of enteral feeding versus parenteral nutrition have shown significantly lower rates of infection when the gut is fed.^{8–9} In addition, studies in animals have shown early feeding to be associated with more rapid maturation of gut associated immune function.¹⁰

In our unit, during recent years, we have gradually started enteral feeding at an earlier age and progressed in larger daily increments. Thus, the purpose of the study was to evaluate the impact of this change on the rate of nosocomial sepsis and NEC in VLBW infants.

METHODS

Setting

This study was conducted in the NICU at Kaplan Medical Center, Rehovot, which is a 27 bed, inborn tertiary unit that provides a full range of neonatal and surgical services. About 5000–5500 infants are delivered annually in the hospital.

To reduce the incidence of nosocomial sepsis, an infection control task force was established during the study period. The group recommended and enforced a range of measures for infection control, such as strict hand washing, the use of disposable gloves and gowns as required, closed airway suction systems, improved antiseptic procedures, careful

isolation of infected infants, and shortened courses of antibiotic treatment. In addition, as of December 1998, in response to increased antibiotic resistance of Gram negative bacteria, the empiric antibiotic treatment for suspected nosocomial sepsis was changed from ceftazidime and amikacin to piperacillin/tazobactam and amikacin.

Definitions

Sepsis with coagulase negative staphylococci was defined as two positive blood cultures taken from two different peripheral sites combined with appropriate clinical signs. For other bacteria, a single positive blood culture was considered sufficient. Nosocomial sepsis was defined as appearing after 72 hours of age.

The severity of the initial disease was assessed using the clinical risk index for babies (CRIB) score.¹¹ NEC was graded as described by Walsh and Kliegman.¹² Intraventricular haemorrhage was graded by the method of Papile *et al*,¹³ and retinopathy of prematurity according to the international classification.¹⁴

Study protocol

A retrospective chart review of VLBW (< 1500 g) infants born during 1995–2001 was performed. Data were collected on the daily amounts of enteral and parenteral nutrition, clinical course, and major morbidity during the NICU stay.

Enteral feeding was started as soon as the infant's condition was considered to be stable by the attending neonatologist. None of the following was considered a contraindication to enteral feeding: mechanical ventilation (endotracheal or nasal), umbilical catheters, low Apgar

Abbreviations: CRIB, clinical risk index for babies; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; VLBW, very low birthweight

scores, small for gestational age, or polycythaemia. Criteria for withholding feeds (attending level decision) were suspected or proven NEC, feeding intolerance (large gastric residuals, abdominal distension), and suspected sepsis. Enteral feeds were begun with either breast milk or a standard preterm formula, and, once the infant reached full feeds, nutritional supplements were added (human milk fortifier, polycose, MCT oil). Parenteral nutrition was begun with glucose (4–6 mg/kg/min), protein, and lipid up to 3 g/kg/day each, and adjusted thereafter as required. In general, the energy intake of full enteral feeding was in the range 100–140 kcal/kg/day and that of parenteral feeding 80–110 kcal/kg/day.

Criteria for exclusion from the study included major congenital malformations, death during the first 48 hours of life (as usually the cause of death is not related to either nosocomial sepsis or NEC), transfer to another unit before discharge home, and missing records.

Statistical analysis

Amounts and day of introduction of enteral and parenteral nutrition were compared between infants with and without nosocomial sepsis, and those with and without NEC.

Categorical variables were compared using the χ^2 test. The means of continuous variables were compared using Student's *t* test, and the data are presented as mean (SD). Correlation between continuous variables was measured using Pearson's correlation coefficient. The influence of relevant confounding variables, identified by univariate analysis, was assessed using multivariate logistic regression analysis.

Bacteriological methods

Blood cultures were tested with a Bactec 9240 system (Beckton Dickenson, Sparks, Maryland, USA) using standard methods. Identification and antibiotic sensitivity testing of the pathogens was performed by a Vitek system (bioMerieux Vitek, Inc, Durham, Missouri, USA). Susceptibility results were interpreted as sensitive, intermediate, or resistant to each antibiotic according to National Committee for Clinical Laboratory Standards guidelines.¹⁵

RESULTS

Study population

During the years 1995–2001, a total of 440 VLBW infants were admitted to the NICU. Fifty five were excluded because of congenital malformations ($n = 14$), death before the age of 48 hours ($n = 24$), transfer to or from another hospital ($n = 15$), and missing records ($n = 2$). None of the VLBW infants who were transferred to another unit or the two infants with the missing records had either NEC or documented sepsis during their stay in our NICU.

The study group included 385 VLBW infants, of whom 163 (42%) developed nosocomial sepsis and 35 (9%) developed NEC. Thirty six infants died after the age of 48 hours.

Infants with nosocomial sepsis were of earlier gestational age (28.5 (2.5) weeks *v* 30.1 (3.2) weeks, $p = 0.0001$) and lower birth weight (1042 (260) *v* 1167 (292) g, $p = 0.0001$), suffered more often from respiratory distress syndrome (RDS) (72% *v* 47%, $p = 0.0001$) and chronic lung disease (11% *v* 45%, $p = 0.00001$), and had higher CRIB scores (5.1 (4) *v* 3.4 (4), $p = 0.0001$). In addition, infants with nosocomial sepsis received more surfactant, mechanical ventilation, umbilical and peripheral catheters, and parenteral nutrition.

No significant differences in delivery type, Apgar scores, sex, incidence of early onset sepsis, and the rate of multiple pregnancies were detected between infants with and without sepsis (table 1).

Enteral and parenteral nutrition

Enteral feeding was started at an earlier age in infants who did not develop nosocomial sepsis (2.8 (2.6) days *v* 4.8 (3.7) days, $p = 0.0001$). They were free of intravenous access earlier (10.9 (8.8) days *v* 23.7 (18.3) days, $p = 0.0001$) and had fewer days on total parenteral nutrition than infants who did develop nosocomial sepsis (8.3 (6) days *v* 20.6 (12) days, $p = 0.0001$). The findings were similar for the subgroup of extremely low birth weight (< 1000 g) infants and those infants with RDS (table 2).

No difference was observed in the incidence of human milk feeds in infants with or without nosocomial sepsis (32% *v* 25%, $p = 0.28$).

Multivariate analysis, including variables that were significant on univariate analysis (table 1), showed age at start of enteral feeding, RDS, and birth weight to be the most significant predictors of risk of nosocomial sepsis ($p = 0.0005$, $p = 0.024$, $p = 0.011$).

Figure 1 shows the annual mean age at introduction of enteral feeding and the incidence of nosocomial sepsis during 1995–2001. The correlation between these variables was significant ($r^2 = 0.89$, $p = 0.007$). In comparison, although RDS and birth weight are predictors of nosocomial sepsis, they did not change throughout the study period.

Enteral feeding and NEC

Enteral feeds were started at the same age in infants with and without NEC: 3.1 (2) *v* 3.7 (3) days, $p = 0.28$. Similar findings were noted in the subgroup of infants with birth weight below 1000 g: 4.2 (2) *v* 4.6 (3) days, $p = 0.68$.

Morbidity

Infants who developed sepsis during their stay in the NICU had significantly higher rates of morbidity—chronic lung disease (O_2 at 36 weeks) (24% *v* 5%, $p = 0.0001$), retinopathy of prematurity (43% *v* 15%, $p = 0.0001$)—and they were discharged at an older age (80 (44) *v* 52 (29) days, $p = 0.0001$). There was no difference between the groups in rate of intraventricular haemorrhage (14% *v* 16%, $p = 0.49$) or mortality (7.4% *v* 10.8%, $p = 0.25$).

Table 1 Descriptive data, morbidity, treatments, and mortality in the nosocomial sepsis and control groups

	Sepsis	No sepsis	p Value
Number	162	223	
Birth weight (g)	1042 (260)	1167 (292)	0.0001*
Gestational age (weeks)	28.5 (2.5)	30.1 (3.2)	0.0001*
SGA	17%	31%	0.007*
CRIB score	5.1 (4)	3.4 (4)	0.0001*
Apgar score (1 min)	6.2 (2.7)	6.7 (2.7)	0.09*
Apgar score (5 min)	8.5 (1.6)	8.8 (1.5)	0.16
Male	51.5%	48.6%	0.58
Caesarean section	71%	71%	0.93
Singleton	58%	53%	0.8
Early sepsis	2%	3%	0.3
RDS	72%	47%	0.00001*
PDA	41%	22%	0.001*
CLD	45%	11%	0.00001*
NEC	18%	7%	0.001*
IVH (all grades)	14%	17%	0.49
Mechanical ventilation (days)	14.9 (16)	6.3 (9.6)	0.0001*
Surfactant (doses)	1.5 (0.8)	1.2 (0.8)	0.003*
TPN (days)	21 (12)	8 (6)	0.0001*

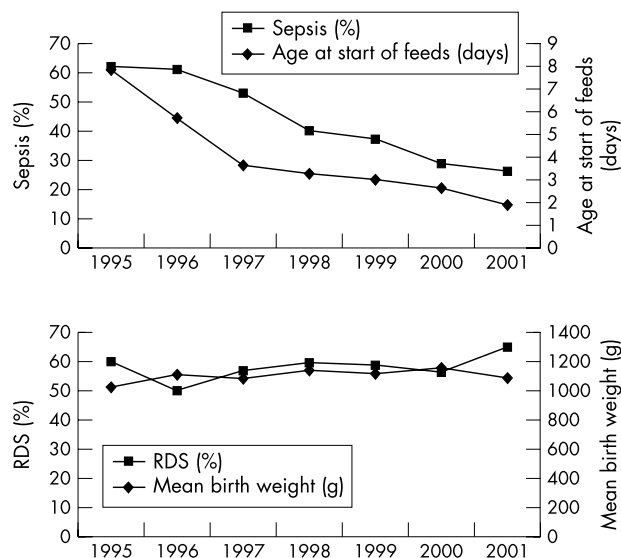
Values are mean (SD) or percentage.

*Variables included in multivariate analysis.

SGA, Small for gestational age; CRIB, clinical risk index for babies; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; CLD, chronic lung disease; NEC, necrotising enterocolitis; IVH, intraventricular haemorrhage; TPN, total parenteral nutrition.

Table 2 Age at start of enteral feeding in very (VLBW) and extremely low birthweight infants with and without nosocomial sepsis and necrotising enterocolitis (NEC) and respiratory distress syndrome (RDS)

	Sepsis (days)	No sepsis (days)	p Value	NEC	No NEC	p Value
Birth weight <1500 g	4.8 (3.7) n = 162	2.8 (2.6) n = 221	0.0001	3.1 (2) n = 32	3.7 (3) n = 322	0.28
Birth weight <1000 g	5.5 (3.7) n = 64	3.2 (2) n = 42	0.001	4.2 (2) n = 13	4.6 (3) n = 93	0.68
VLBW infants with RDS	5.2 (3.5) n = 110	3.8 (3.3) n = 87	0.006	—	—	—

**Figure 1** Mean annual incidence of nosocomial sepsis, age at start of enteral feeding, mean annual birth weight and incidence of respiratory distress syndrome (RDS) 1995–2001.

DISCUSSION

In this study, early enteral feeding, starting at the second or third day of life, appeared to be associated with a reduced risk of nosocomial sepsis without incurring an increased risk of NEC.

This study, when taken together with other recent work, suggests that the potential benefit of less sepsis outweighs the potential but unproven risk of NEC. In fact, there is mounting evidence for the decreased significance of enteral feeding in the pathogenesis of NEC. Rayyis *et al*¹⁶ compared slow feeding advancement (15 ml/kg/day) with fast feeding advancement (35 ml/kg/day) in VLBW infants and found no difference in the incidence of NEC. Ostertag *et al*¹⁷ attempted to determine the optimal time for initiating enteral feeds in VLBW sick infants. They found no difference in the incidence of NEC between early enteral feeding starting on day 1 of life compared with day 7 of life. Davery *et al*¹⁸ compared early (2 days) versus late (2–5 days) enteral feeding in VLBW infants and likewise found no difference between the groups.

An alternative approach is to begin early trophic feeding, in which only small volumes of 0.5–1 ml/kg/h are begun within the first days of life and increased later when the infant's condition is considered stable. Trophic feeding combines an attempt to overcome the lack of gastrointestinal stimulation during total parenteral nutrition with minimal stress to the ill infant.¹⁹ This has been tried successfully and without an increase in the risk of intestinal complications.

Possible mechanisms involved in the decrease in the rate of infection with early enteral feeding include:

(1) Prevention of gastrointestinal atrophy: animal studies show that gastrointestinal atrophy develops within two to three days of fasting even in those kept in

positive nitrogen balance. This appears to be because enterocytes rely on the gastrointestinal luminal content for nutrition.²⁰

- (2) Intestinal bacterial contamination: the absence of enteral feeding leads to an alteration in gut flora allowing the overgrowth of enteropathogenic species.²¹ In addition, Garcia-Lafuente *et al*²² showed that single-organism colonisation of an isolated loop of rat intestine induced changes in permeability that facilitate bacterial translocation into the bloodstream.
- (3) Early feeding allows decreased use of total parenteral nutrition. Total parenteral nutrition has been shown to have an immunosuppressive effect. Okada *et al*^{23, 24} have shown that when it is administered for more than two weeks it impairs the phagocytosis and killing of coagulase negative staphylococci, and that introduction of small volumes of enteral feeding improved this finding.
- (4) Earlier enteral feeding results in a decreased need for intravenous devices and thus less insult to the skin and less opportunity for the entry of pathogenic organisms.
- (5) Mucosal immunity: the source of most mucosal immunity in humans is from gut associated lymphoid tissue in the Payer's patches of the small intestine. Neonates are born without any appreciable gut associated lymphoid tissue, but it slowly increases to normal levels over the first two years of life. There is evidence to suggest that early feeding, particularly colostrum and human milk, may promote the development of specific immune function in association with the gut associated lymphoid tissue.^{25, 26} The possible significance of this mechanism in preterm infants is as yet unclear.

Retrospective studies may point to correlations between events and thus serve as the basis for hypotheses. Although many factors, including infection control measures, may have been important, this study appears to suggest that feeding preterm infants earlier may help to reduce the risk of infection. The multivariate analysis and correlation over time between earlier feeding and less sepsis support this evidence. However, large randomised trials are required to provide conclusive evidence that it is safe and beneficial to start enteral feeding early in preterm infants.

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