Impact of Optimized Breastfeeding on the Costs of Necrotizing Enterocolitis in Extremely Low Birthweight Infants

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Objective To estimate risk of necrotizing enterocolitis (NEC) for extremely low birth weight (ELBW) infants as a function of preterm formula (PF) and maternal milk intake and calculate the impact of suboptimal feeding on the incidence and costs of NEC.

Study design We used aORs derived from the Glutamine Trial to perform Monte Carlo simulation of a cohort of ELBW infants under current suboptimal feeding practices, compared with a theoretical cohort in which 90% of infants received at least 98% human milk.

Results NEC incidence among infants receiving ≥98% human milk was 1.3%; 11.1% among infants fed only PF; and 8.2% among infants fed a mixed diet (P = .002). In adjusted models, compared with infants fed predominantly human milk, we found an increased risk of NEC associated with exclusive PF (aOR = 12.1, 95% CI 1.5, 94.2), or a mixed diet (aOR 8.7, 95% CI 1.2-65.2). In Monte Carlo simulation, current feeding of ELBW infants was associated with 928 excess NEC cases and 121 excess deaths annually, compared with a model in which 90% of infants received ≥98% human milk. These models estimated an annual cost of suboptimal feeding of ELBW infants of $27.1 million (CI $24 million, $30.4 million) in direct medical costs, $563 655 (CI $476 191, $599 069) in indirect nonmedical costs, and $1.5 billion (CI $1.3 billion, $1.6 billion) in cost attributable to premature death.

Conclusions Among ELBW infants, not being fed predominantly human milk is associated with an increased risk of NEC. Efforts to support milk production by mothers of ELBW infants may prevent infant deaths and reduce costs. *(J Pediatr 2016;175:100-5)*.

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Among extremely low birth weight (ELBW) infants (birthweight ≤1000 g), receiving mother's own milk is associated with lower rates of in-hospital morbidity, including lower rates of necrotizing enterocolitis (NEC)[1-5] and late-onset sepsis.[1,2] Mother's milk exposure in the first 14 days of life is associated with a lower incidence of the composite outcome of NEC or death prior to hospital discharge.[6] Human milk diets also are associated with shorter hospital stays[1] and lower incidence of rehospitalization[7] than diets that include cow's milk-based preterm formula (PF). Moreover, institutional costs for providing PF are higher than for human milk.[8]

Rates of breastfeeding initiation have increased among mothers of ELBW infants,[9] yet in the neonatal intensive care unit (NICU) setting, mothers are sometimes unable to supply milk.[8] Thus, the typical NICU diet for ELBWs currently consists partially of human milk and partially of PF or donor human milk. However, mothers who receive breast pumps, supplies, and intensive support can meet most of their infants' nutritional needs during the first month of life.[8,10]

ELBW	Extremely low birth weight
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PF	Preterm formula
PMA	Postmenstrual age
VLBW	Very low birth weight
VON	Vermont Oxford Network

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The purpose of this study was to estimate the cost and mortality savings that might be realized if all NICUs provided intensive support for mothers of ELBW infants and achieved optimal NICU feeding patterns (near exclusive human milk) for 90% of US ELBW infants.

Methods

We developed models of the medical and mortality costs of NEC under current and optimized (defined as 90% of infants receiving ≥98% human milk) feeding patterns, and calculated the savings achieved by an optimized diet.

We measured direct and indirect medical costs, indirect nonmedical costs (eg, parental travel), and cost because of death from NEC, following previous analyses.[11,12] These models assumed that all infants received human milk fortified with bovine-based fortifier and were supplemented with PF if human milk was not available; our model did not consider use of donor human milk or donor milk-derived human milk fortifier.

We performed a secondary analysis of the National Institute of Child Health and Human Development Glutamine Trial dataset to calculate the NEC burden in ELBW infants fed predominantly human milk compared with those fed mixed PF and human milk diets or exclusive PF diets. The Glutamine Trial prospectively enrolled infants admitted at birth from 15 centers of the National Institute of Child Health and Human Development Neonatal Research Network between October 1999 and August 2001, with birth weights 400-1000 g.[13] We analyzed the subset of 848 infants who were alive and hospitalized at a Neonatal Research Network center at 36 weeks postmenstrual age (PMA) and for whom full data were available on enteral feedings and intake through 36 weeks PMA.[7] We chose 36 weeks PMA to be most inclusive of NEC incidence in ELBW infants.[14] No participating centers used donor human milk during this trial; all human milk intake was human milk. Fortification with bovine-derived fortifier was standard of care for all infants.

Human milk intake was calculated as the proportion of all enteral intake throughout the study period. We defined optimized feeding as receiving the vast majority of enteral intake as human milk, while excluding infants given very little enteral feeding. Infants with optimized feeding were those who received the highest quintile of human milk intake, which was ≥98% of all enteral intake. Comparison groups were infants receiving exclusively PF and those receiving a mixed diet with <98% human milk.

Incidence of NEC, ≥Bell stage II, was collected on all subjects. aORs were calculated for NEC among infants fed PF compared with infants fed mixed or optimized diets using logistic regression modeling, adjusting for receipt of antenatal steroids, birth weight, gestational age, and study center. SAS 9.3 (SAS Institute, Cary, North Carolina) was used for analyses.

Because the Glutamine Trial analysis only included NICU survivors, we estimated NEC mortality using rates from the Vermont Oxford Network (VON),[15] which were highly consistent with national rates[16,17] and indicated that net NEC mortality was 13.4% for infants 500-1000 g. The incidence of NEC in the VON dataset was similar to the Glutamine Trial population (11.6% in VON vs 10.2% in the Glutamine Trial). We assumed that mortality would be equally likely once an infant developed NEC regardless of infant feeding.

For estimates of feeding patterns of ELBW infants, we used data reported from a prospective single center cohort study of over 400 very low birth weight (VLBW) infants in Chicago, Illinois.[18-20] NEC incidence in that population of ELBW and larger VLBW was 7%, and 24.2% of VLBW infants received exclusive human milk at NICU discharge.[10] We used these data to estimate current rates of ELBW infants receiving ≥98% human milk through 36 weeks PMA. For the remaining 75.8% of ELBWs, we used data from the Glutamine Trial to estimate that 67.9% of ELBWs are currently fed a mixed diet and 8.2% of ELBW are exclusively fed PF.

We defined optimized feeding in the ELBW population as 90% of all ELBW infants receiving ≥98% human milk from birth through 36 weeks PMA. We assumed 90%, rather than 100%, to account for those mothers who are biologically or medically unable to provide milk,[21] and did not include mothers whose use of illicit substances resulted in mother's milk being contraindicated per hospital policy.[22]

To calculate direct medical costs, we used marginal direct hospital costs for medical and surgical NEC reported by Johnson et al,[23] plus 15% hospital overhead from the Centers for Medicare and Medicaid[24]: $16 670 and $28 334, respectively. To this we added physician fees based on national Medicare daily neonatologist reimbursement rates[25] and a projected incremental length of stay of 17 days for NEC infants compared with preterm infants without NEC. Using 2014 US$ dollars, total direct medical costs were $23 423 (medical) NEC and $35 088 (surgical) NEC. For indirect nonmedical costs, we used a previously reported estimate of parental nonmedical expenditure during the neonatal period ($3604) and divided by the NICU stay (106 days) to derive a daily parental cost ($34), which was multiplied by the 17 excess days for a total indirect NEC cost of $578. All costs from preexisting studies were inflated from their original dollar value to 2014 US$ dollars using the consumer price index for all goods[26] (**Table I**). We estimated the cost of premature death because of NEC at $12.03 million in US$ 2014 dollars, the value of a statistical life commonly used by government agencies to determine cost-effectiveness of policies to reduce mortality risk.[27]

We created a population of simulated infants born between 23 and 32 weeks gestational age, with birth weights of 400-1000 g sourced from 2012 US vital statistics data. We followed this simulated population from birth through 36 weeks PMA, to simulate the highest risk period for NEC.[14] We excluded infants who died in the first 72 hours of life, using linked vital statistics data.[28] We performed 2 Monte Carlo simulations, one using current, (suboptimal) and one using optimized feeding patterns for ELBW infants.