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## Impact of suboptimal breastfeeding on the healthcare and mortality costs of necrotizing enterocolitis in extremely low birthweight infants

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### Abstract

**Objective**—To estimate risk of NEC for ELBW infants as a function of preterm formula and maternal milk (MM) intake and calculate the impact of suboptimal feeding on NEC incidence and costs.

**Design**—We used adjusted odds ratios (aORs) derived from the Glutamine Trial to perform Monte Carlo simulation of a cohort of ELBW infants under current suboptimal feeding practices, compared to a theoretical cohort in which 90% of infants received at least 98% MM.

**Results**—NEC incidence among infants receiving 98% MM was 1.3%; 11.1% among infants fed only preterm formula; and 8.2% among infants fed a mixed diet ( $p=0.002$ ). In adjusted models, compared with infants fed predominantly MM, we found an increased risk of NEC associated with exclusive preterm formula (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

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infants received 98% MM. These models estimated an annual cost of suboptimal feeding of ELBW infants of \$27.1 million (CI \$24million, \$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 MM 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.

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## BACKGROUND

Among Extremely Low Birth Weight (ELBW, birthweight < 1000 g) infants, receiving mother's own milk (MM) is associated with lower rates of in-hospital morbidity, including lower rates of necrotizing enterocolitis (NEC) (1-5) and late-onset sepsis.(1, 2) MM 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 in this population.(6) MM diets are also associated with shorter hospital stays (7) and lower incidence of re-hospitalization(8) than diets that include cow's milk based preterm formula (PF). Moreover, institutional costs for providing PF are higher than for MM (9).

Rates of breastfeeding initiation have increased among mothers of ELBW infants,(10) yet in the neonatal intensive care unit setting (NICU), mothers are sometimes unable to supply the milk their infant needs.(9) Thus, the typical NICU diet for ELBW infants currently consists partially of MM and partially of PF or donor human milk. However, mothers who receive intensive support, breast pumps and supplies, can meet most of their infants' nutritional needs during the first month of life (9, 11).

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 optimal NICU feeding patterns (near exclusive MM) were achieved for 90% of U.S. ELBW infants.

## METHODS

We developed models of the medical and mortality costs of NEC under current (suboptimal) and optimal NICU infant feeding patterns, and calculated the savings that could be achieved by optimizing ELBW infants' intake of MM. We defined an optimal NICU diet as 90% of infants receiving 98% MM. We measured direct and indirect medical costs, indirect non-medical costs (e.g. parental travel), and cost due to death from NEC for optimal and suboptimal infant feeding, following previous analyses. (12, 13) These models assumed that all infants received MM fortified with bovine-based fortifier, and were supplemented with PF if MM was not available; our model did not consider use of donor human milk or donor milk derived human milk fortifier.

To create these models, we specified multiple parameters as described below.

### NEC incidence in ELBW infants by infant feeding

We performed a secondary analysis of the NICHD Glutamine Trial dataset to calculate the NEC burden in ELBW infants fed diets of predominantly MM compared to those fed mixed PF and MM diets and those fed exclusive PF diets. The Glutamine Trial prospectively enrolled infants admitted at birth from 15 centers of the NICHD Neonatal Research Network (NRN) between October 1999 and August 2001, with birth weights 400-1000g. The details of this study were previously reported (14). Enteral intake data were collected on all subjects (8). Included in this analysis was the subset of 848 infants who were alive and hospitalized at an NRN center at 36 weeks postmenstrual age (PMA) and for whom full data were available on the composition of enteral feedings. We used enteral intake data from birth through 36 weeks PMA for this analysis. Although NEC incidence has been shown to peak between 31 and 33 weeks PMA, cases continue to occur beyond this time point(15). We chose 36 weeks PMA to be most inclusive of NEC incidence in ELBW infants(15). No participating centers used donor human milk during this trial; all human milk intake was MM. Fortification with bovine derived fortifier was standard of care for all infants.

MM intake was calculated as the proportion of all enteral intake throughout the study period, and total volume of MM fed during the study period was determined. We defined optimally fed infants as those who both received the vast majority of their enteral intake as MM and received a high volume of MM. This definition was chosen to exclude from the optimal group infants who were given very little enteral feeding, but for whom that small volume was all MM. We specified as optimally fed infants those who received the highest quintile of MM intake among all subjects. In this quintile, 98% of all enteral intake was MM. This group of infants was compared to infants receiving exclusively PF, and those receiving a mixed diet that included < 98% MM. Although a truly optimal NICU diet is 100% MM, this was rare in the dataset, making modeling unstable.

Incidence of NEC, Bell's Stage II, was collected on all subjects. We calculated and compared NEC incidence for groups of infants receiving 98% MM, infants receiving exclusively PF, and those receiving < 98% MM. Adjusted Odds Ratios (aORs) were calculated for NEC among infants fed PF compared to infants fed a mixed diet that was < 98% MM or those fed predominately MM (98% MM) using logistic regression modeling, adjusting for receipt of antenatal steroids, birth weight, gestational age, and study center. SAS 9.3 (SAS Institute, Cary, NC) was used for analyses.

### NEC Mortality in ELBW infants

Because the Glutamine Trial analysis only included NICU survivors, we estimated NEC mortality using the rates from the Vermont Oxford Network (VON)(16) which were highly consistent with coded mortality data for NEC from the National Center for Vital Statistics during the years these data were collected,(17, 18) and indicated that net NEC mortality was 13.4% for infants 500-1000 g. Additionally, incidence of NEC in this VON dataset was very similar to that in the Glutamine Trial population we studied (11.6% in VON vs. 10.2% in the Glutamine Trial). We conservatively assumed that mortality would be equally likely once an infant developed NEC regardless of infant feeding, as there were no published data available regarding differential NEC mortality by infant diet.

### Current Feeding of ELBW infants

For current estimates of feeding of ELBW infants, we used data reported from Rush University Medical Center in Chicago, IL,(19, 20) who recently published a prospective cohort study of over 400 VLBW infants which specifically evaluated the impact of MM on those infants' outcomes (21). NEC incidence in the population studied was 7%, and the population included both ELBW and larger VLBW infants. At Rush, 24.2% of VLBW infants were receiving exclusive MM at NICU discharge (11), which we used to conservatively estimate current rates of ELBW infants receiving 98% MM through 36 weeks postmenstrual age. For the remaining 75.8% of ELBWs, we used data from the Glutamine trial to estimate the proportion receiving a mixed diet or exclusive PF; under these assumptions, we estimated 67.9% of ELBWs are currently fed a mixed diet and 8.2% of ELBW are exclusively fed PF.

### Optimal Feeding of ELBW infants

We assumed optimal feeding in the ELBW population as 90% of all ELBW infants receiving 98% MM from birth through 36 weeks postmenstrual age; we assumed 90%, rather than 100%, to account for the proportion of mothers who are biologically unable to provide milk or for whom doing so is medically contraindicated (22). Our estimate of 90% does not include mothers whose use of illicit substances such as cocaine, methamphetamine, and cannabis may result in mother's milk being contraindicated per hospital policy. Although estimates of the prevalence of use of these substances during pregnancy are available for the entire population of pregnant women (23), continuation of use after delivery and what proportion of those mothers provide milk is unknown. Therefore, we did not include an estimate of mothers unable to provide milk due to substance use.

### Cost Estimates for NEC and NEC mortality

To calculate direct medical costs, we used marginal direct hospital costs for medical and surgical NEC reported by Johnson et al(24), which were retrieved directly from the cost accounting system of Rush University Medical Center, plus 15% hospital overhead (source: Centers for Medicare and Medicaid):(25) \$16,670 and \$28,334 respectively. To this we added physician fees based on an incremental length of stay of 17 days for NEC infants compared with preterm infants without NEC, which was the increase in length of stay reported by Johnson et al(24). We used the national Medicare daily neonatologist reimbursement rates (26) assuming 2014 US\$ dollars (\$6,754 total excess physician cost), for total direct medical costs of \$23,423 (medical) NEC and \$35,088 (surgical) NEC. For indirect non-medical costs (e.g. travel costs) we used a previously reported estimate of parental non-medical expenditure during the neonatal period. We took this reported estimate (\$3,604) and divided by the NICU stay (106 days) for infants in that study to get a daily parental cost (\$34). We then multiplied this cost by the 17 excess days for NEC to get 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 (CPI) for all goods (27). (Table 2) .

We estimated the cost of premature death due to NEC at \$12.03 million in US\$ 2014 dollars, the value of a statistical life (VSL) commonly used by government agencies to determine cost-effectiveness of policies to reduce mortality risk (28).

### Model and Simulations

We created a population of simulated infants born between 23 and 32 weeks' gestational age, with birth weights of 400-1000g sourced from 2012 US vital statistics data. We followed this simulated population from birth through 36 weeks postmenstrual age, to simulate the highest risk period for NEC (15). We excluded infants who died in the first 72 hours of life, using linked vital statistics data (29). We performed two Monte Carlo simulations, one using current, (suboptimal) and one using optimal feeding patterns for ELBW infants. We modeled NEC incidence and odds ratios using the triangular distribution. The mode was set to the point estimate, the maximum was set to the upper value of the 95% confidence interval, and the minimum was set to the lower value of the 95% confidence interval (see Table 1). The difference in outcomes (NEC incidence and NEC deaths) for the two simulation cohorts represents the potential savings that could be accrued by increasing use of MM to 90% if observed associations between MM feeding and NEC outcomes are causal. See figure 1 for model schematic. Java™ SE Runtime Environment build 1.7.0\_05-b06 was used to create both models.

## RESULTS

### NEC and diet in the Glutamine Trial

Our sample from the Glutamine Trial included 848 ELBW infants, 650 of whom received at least some MM, 198 of whom were fed exclusive PF. Among those infants receiving any MM, 77 received ≥98% MM (optimal), 573 received <98% MM (mixed) and 198 received exclusive PF. Gestational age varied between diet groups, with the optimal group being 6 days less mature (optimal 25<sup>3/7</sup> weeks, mixed diet 26<sup>2/7</sup> weeks, PF 26<sup>2/7</sup> weeks,  $p = 0.003$ ). The highest quintile of MM intake for the study period was >6533 ml. The incidence of NEC among 14 centers ranged from 4.6% to 18.6%. One center, (n=14 infants) had a 0% incidence of NEC, and thus this center was excluded from all adjusted analyses. 87 cases of NEC occurred, 50% medical NEC and 50% surgical NEC. 77 infants were included in the optimal group (≥98% MM) one of whom developed NEC (1.3%, 95% CI <0.0001-7.7%). In contrast, incidence of NEC was 11.1% (95% CI 7.4-16.3%) among the 198 infants who received exclusive PF (no MM) and 8.2% (95% CI 6.2-10.8%) among the 573 infants who were fed a mixed diet, defined as receiving any MM (Table 1). Adjusted for center, gestational age, infant birthweight, sex, and receipt of antenatal steroids, infants who received exclusive PF were more likely to develop NEC (aOR=12.05, 95% CI 1.54, 94.17), as were infants fed a mixed diet (aOR 8.68, 95% CI 1.15-65.24), compared with infants fed ≥98% MM. There was no significant difference in the odds of NEC among infants fed a mixed diet compared with those exclusively fed PF (aOR 1.39, 95% CI 0.83, 2.33).

### Economic Modeling

Using the 2012 US population dataset, we estimate that 928 (CI 830, 1036) excess cases of NEC are associated with suboptimal breastfeeding. In the optimal breastfeeding model, NEC

deaths were reduced by 51% compared with the suboptimal model, with 121 (CI 108, 134) fewer deaths (Table 2).

The total direct medical excess cost of NEC among ELBW infants was \$27.1 million (CI \$24 million, \$30.4 million), the total indirect non-medical excess cost was \$563,655 and (CI \$476,191, \$599,069) the total excess cost of NEC death was \$1.5 billion (CI \$1.3 billion, \$1.6 billion) (Table 2). The CIs represent the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of these distributions.

## DISCUSSION

We found that ELBW infants fed diets containing exclusive PF faced markedly increased risk of NEC, compared with those fed 98% MM. We were surprised to find no difference in NEC rates among infants fed exclusively PF and those who received a mixed diet containing <98% MM; this suggests that mixed MM and PF diets are not as protective against NEC as complete MM diets, however we were not able to model mixed diets more precisely. Other investigators have found that NEC risk decreases as MM exposure increases (6), and that diets containing > 50% MM are protective compared with those containing < 50% MM (5).

Our findings confirm and extend earlier work on the importance of MM feeding for ELBW infants and NEC-associated morbidity, mortality, and costs. Earlier studies have found that MM feedings in the NICU are associated with reduced NEC morbidity and mortality(1-6). Our work extends these findings in a recent US cohort of infants with detailed, prospective data on dose of MM ingested. Our economic analysis extends the current literature through a Monte Carlo simulation to estimate the confidence intervals around predicted costs and mortality rates across a contemporary population of ELBW infants.

As with any simulation, our results are a function of the quality of the data available regarding current disease prevalence, NICU feeding practices, and costs associated with medical and surgical NEC. As there are no population-based studies that measure ELBW infant feeding, incidence of NEC, and NEC mortality among infants from 500-1000 g, we extrapolated inputs to our model from several sources.

Our definition of optimal breastfeeding represents an ideal far from our current practice, and one could argue that it is unattainable for a variety of reasons, representing a limitation of our study. If we consider lactation support for mothers of ELBW infants at Rush University Medical Center to represent the best current practice, the gap between optimal and current is large (24% current, 90% optimal). We did not model the effects of lower levels of breastfeeding, and our results should not be interpreted to refer to any condition other than what we have specified. The use of Rush Medical Center data for our estimates of current feeding practices may also overestimate the proportion of ELBW infants currently receiving nearly exclusive MM through 36 weeks postmenstrual age. In the Glutamine Trial, 9% of infants met these criteria. However, human milk use has increased substantially in the decade since, making the true number likely between the two estimates. If our estimate for current feeding is high, it would reduce our estimate of the cost of suboptimal breastfeeding, thus our use of 24% represents a conservative choice.



Moreover, data regarding appropriate costs attributable to surgical and medical NEC are limited. We used conservative direct cost estimates in our model, which are lower than what is often cited in the literature. While we included additional neonatologist physician cost attributable to NEC, we did not have information regarding surgical physician care, so that is not included, lowering our NEC cost estimates. Other sources have used numbers that are multifold higher (30, 31), for example \$74,004 for incremental costs medical NEC and \$198,040 for surgical NEC in 2011 dollars (30). However, these other sources used cost measures that are less precise than the micro-costed values used in this analysis (32). We further assumed equal rates of surgical and medical NEC, based on our finding that they occurred equally frequently in our ELBW dataset, similarly to the findings of Hull et al, who reported an incidence of 52% surgical NEC in a cohort of 17, 159 NEC cases in ELBW infants in the VON (33).

A recent report by Johnson et al of the cost savings of use of maternal milk in the first 14 days of life among VLBW infants reported a marginal increase in medical cost of \$43, 818 per case of NEC (34), higher than the cost estimates used in our study. However, this analysis did not adjust the increased cost of NEC for the presence of other morbidities of prematurity, in contrast to their earlier work, from which we drew our estimate of \$23,423 additional cost per case of medical NEC and \$35,088 per case of surgical NEC. Johnson and colleagues also modeled the effects of maternal milk use during only the first 14 days of life, in contrast to our study that included maternal milk use from birth through 36 weeks postmenstrual age, a longer risk period for NEC. Interestingly, they also found that exposure to any formula in the first 14 days increased the risk of NEC (OR 3.47, 95% CI 1.22-9.92,  $p = 0.02$ ), and that infants both with and without NEC had similar cumulative MM intake in the first 14 days (80% in NEC infants and 81% in non-NEC infants). The overall incidence of NEC reported (10%) was similar to that of the entire Glutamine Trial population used in our study (10.2%), although the Glutamine Trial population was limited to infants less than 1000g at birth, rather than those up to 1500g. Johnson's analysis adds additional pieces to the puzzle of NEC and MM, but we cannot compare results directly with ours because there was no separate analysis by exclusive human milk use.

We did not have access to data regarding all other risk factors for NEC occurring in the Glutamine Trial dataset, so our results may be affected by unmeasured residual confounding. We were able to adjust for some variables known to be related to risk of NEC, including gestational age, birth weight, sex, and receipt of antenatal steroids (35-37). However, data were not available about use of H2 blocking agents or duration antibiotic use, both of which have been associated with increased risk of NEC in the ELBW population (36, 38). If these agents were used more often in conjunction with increasing formula use, our cost estimates may not be accurate. The multi-center nature and relatively large size of our study population may overcome this limitation to some degree.

Our study is also limited by not considering donor human milk. Results of ongoing trials of donor human milk versus PF will inform future efforts to optimize NICU diets. Findings from these ongoing trials will also enhance the development of cost models that explore infant diet compositions. Our current study is additionally limited by the specificity of the definition of MM and feeding metrics used in other studies. In addition, the Glutamine Trial



used bovine-fortification for MM diet; emerging evidence suggests that fortifier derived from donor human milk might further improve health outcomes by avoiding exposure to bovine protein.(39, 40) Due to differences in study populations and NEC incidence reported in the human milk-derived fortifier studies (35, 3236), we cannot accurately estimate the potential additional beneficial effects of this intervention. These randomized multicenter studies, one of VLBW infants whose mothers intended to breastfeed, and one of those who provided no milk, did not report the exact proportion of subjects' diets that were MM, donor human milk, or preterm formula, and did not report results for the ELBW population separately. Future studies, including randomized trials of fortifier derived from donor human milk compared to bovine-derived fortifier among infants fed otherwise identical MM diets, will be needed to determine if additional cost savings could be realized with the complete removal of bovine protein.

Our results suggest that investing in the basic supplies required to help mothers produce MM for their ELBW infants (e.g., hospital-grade breast pump, pump kit, and hospital food-grade containers) would be extremely cost effective. From previous research,(9) the cost of investing in supporting mothers to produce MM ranges from \$0.53 to \$2.65 per 100 mL (inflated to 2014 US Dollars using the CPI). As noted previously, this is less than the cost of 100 ml of PF (\$3.28) or the cost of 100 ml of donor human milk (\$15.47). Using the Glutamine Trial data, a reasonable estimate of total volume of in-hospital enteral intake in ELBW infants of 6.5L (the lower limit of the highest quintile of enteral intake in the study population) can be made. Using this volume estimate, the cost of optimal feeding is between \$34 and \$172 per infant, compared with formula at \$213 and donor human milk at \$1005 per infant. Using 2012 US vital statistics data, provision of supplies for all mothers of ELBW infants to express milk would cost between \$821,000 and \$ 4.2 million, which compares favorably with the \$31.5 million excess direct medical cost due to NEC.

It should be noted that the cost of investing in supplies for mothers of ELBW infants does not include the cost of maternal time to express milk. In prior work, we found that mothers spent an average of 98 minutes per day expressing milk for their ELBW infants (9). Future research should explore the extent to which investments in supporting mothers, such as extended and paid family leave, reduce costs associated with NEC. Milk production is enhanced by skin-to-skin contact with one's child (41) and may be compromised by separation from one's child and by stress, such as fulfilling work obligations while one's child is critically ill (42, 43). Our results suggest that alleviating these stressors by supporting mothers financially throughout the infant's NICU stay may be cost effective.

Further, investing in MM would reduce the need for donor human milk, which is a limited resource. Donor human milk is currently used as an alternative diet when MM is unavailable; because some important properties of fresh MM are affected by freezing and pasteurization, (44) donor human milk appears to have health outcomes intermediate in efficacy between MM and PF (45, 46). The estimated cost of providing donor human milk to all US ELBW infants is also much higher than the cost of supporting mothers to produce MM, \$24.2 million vs. \$821,000 - 4.2 million annually.

## CONCLUSION

We found that optimal feeding, defined as 98% maternal milk is associated with a reduced risk of NEC among ELBW infants. Our model suggests that the medical and mortality-associated costs of NEC can be reduced with increased MM feeding of ELBW infants. Identifying effective strategies to enable mothers to provide milk for their preterm infants is a major public health priority.

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Authors' contributions

Dr. Tarah Colaizy conceived of the study design and drafted the manuscript. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr. Melissa Bartick designed the economic analysis and helped draft the manuscript. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Brittany Green created the computer model that ran the simulations.

Dr. Andrew Schaefer supervised Brittany Green's computer modeling.

Arnold Reinhold helped conceive of the economic analysis, assisted with the computer and mathematical analysis, and contributed to the manuscript.

Dr. Briana Jegier contributed to the economic analyses and provided cost data for the economic costs of NEC, as well as data and insights from her experience at Rush Medical Center's program to support mothers' efforts to provide their own milk.

Dr. Debra Bogen contributed conceptually to the framing of the study, creation of the model, and its overall design and presentation.

Dr. Eleanor Bimla Schwarz contributed conceptually to the framing of the study and its overall design and presentation and critical review of the manuscript.

Dr. Alison Stuebe contributed substantially to designing the model and decision tree for the outcomes for breastfed versus non-breastfed infants and to identification of race-specific birth and mortality to use for the model and also to critical review of the manuscript.

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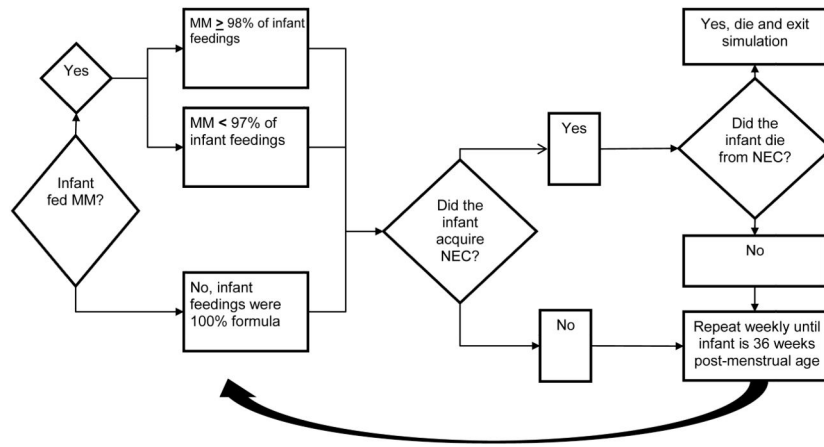
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**Figure 1.**  
Diagram of Markov modeling for ELBW infant NEC outcome



**Table 1**

Assumptions used in the model for necrotizing enterocolitis (NEC) among very low birth weight (ELBW; 1000 g) infants\* by data source.

	Exclusive PF	Mixed diet (<98% MM)	Predominately MM ( 98% enteral feeds)	Cost Estimates
<b>Glutamine Trial* (courtesy of the Neonatal Research Network)</b>				
Number of infants per group (total n=848)	198	573	77	
Number of infants with NEC	22	47	1	
Percentage with NEC (95% CI)	11.1% (7.4-16.3%)	8.2% (6.2-10.8%)	1.3% (<000.1-7.7%)	
<b>Vermont Oxford Network</b>				
Mortality attributable to NEC for infants 1000 g	13.4%	15.6%	14.2%	
<b>Rush University Medical Center</b>				
Current infant feeding rates assumed by the model for all ELBW infants	8.2%	67.6%	24.2%	
Total hospital medical cost per NEC case (direct marginal cost plus 15% overhead)				\$16,670
Total hospital surgical cost per NEC case (direct marginal cost plus 15% overhead)				\$28,334
<b>Other</b>				
Total physician cost per NEC case for excess hospital days due to NEC				\$6,754
Total parental non-medical cost per NEC case for excess hospital days due to NEC				\$578
Total death cost per NEC death				\$12.0 million

\*ELBW infants born 23-32 weeks gestation who lived >72 hours of age

**Table 2**

Excess NEC and NEC mortality incidence and cost for ELBW infants under suboptimal feeding condition

	<b>400-1000g infants n = 24,149</b>
Excess NEC cases under suboptimal feeding condition, (95% CI) *	928 (830, 1036)
Excess NEC deaths under suboptimal feeding condition, (95% CI)	121 (108, 134)
<b><u>Medical NEC</u></b>	
Direct medical ** cost	\$10.9 million (\$9.2 million, \$12.6 million)
Indirect non-medical cost	\$269,068 (\$226,584, \$312,106)
<b><u>Surgical NEC</u></b>	
Direct medical ** cost	\$16.2 million (\$13.6 million, \$19 million)
Indirect non-medical cost	\$267,587 (\$224,546, \$312,738)
<b><u>Death</u></b>	\$1.5 billion (\$1.3 billion, \$1.6 billion)

\* The CIs represent the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles

\*\* Direct medical cost is physician cost plus hospital cost (direct marginal cost + 15% overhead)

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