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### Among extremely low birth weight infants, exclusive maternal feeding decreases necrotizing enterocolitis risk, mortality and health costs

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**English key words:** infant, extremely low birth weight; necrotizing enterocolitis.

**Spanish key words:** recién nacidos de peso extremadamente bajo al nacer; enterocolitis necrotizante.

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# Among extremely low birth weight infants, exclusive maternal feeding decreases necrotizing enterocolitis risk, mortality and health costs

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## Abstract

**Authors' conclusions:** among premature infants, exclusive breastfeeding is associated with a reduced risk of necrotizing enterocolitis (NEC) and death due to NEC, with lower health costs.

**Reviewers' commentary:** according to the results exclusive maternal feeding in extremely low birth weight infants would decrease incidence and mortality of NEC and health costs. The relevance of these results is diminished by the weaknesses of the design and the difficulty of taking it to the habitual practice to obtain the feeding with exclusive breast milk. The real economic efficiency of efforts to support breastfeeding in these children remains to be determined.

**Key words:** infant, extremely low birth weight; necrotizing enterocolitis.

**En los prematuros extremos, la lactancia materna exclusiva disminuye el riesgo, la mortalidad y los costes de la enterocolitis necrotizante**

## Resumen

**Conclusiones de los autores del estudio:** entre los prematuros extremos, la alimentación exclusiva con leche materna se asocia con un menor riesgo de enterocolitis necrotizante (ECN) y de muerte por ECN, y con menores costes sanitarios.

**Comentario de los revisores:** según los resultados, la alimentación materna exclusiva en recién nacidos de peso extremadamente bajo al nacer disminuiría la incidencia y mortalidad por enterocolitis necrotizante y los costes sanitarios. La relevancia de estos resultados queda disminuida por las debilidades del diseño y la dificultad de llevarlo a la práctica habitual para conseguir la alimentación con leche materna exclusiva. Queda por tanto determinar la eficiencia económica real de los esfuerzos para apoyar la lactancia materna en estos niños.

**Palabras clave:** recién nacidos de peso extremadamente bajo al nacer; enterocolitis necrotizante.

## STRUCTURED ABSTRACT

**Objective:** To estimate the costs and decrease in mortality that could be achieved at Neonatal Intensive Care Units (NICUs) if the intake of at least 90% of extremely low birth weight (ELBW) infants was at least 98% human milk.

**Study design:** economic study by means of Markov Chain Monte Carlo (MCMC) simulation modelling.

**Setting:** hospital-based study.

**Study population:** simulated population ( $n = 24\,149$ ) sourced from 2012 United States vital statistics data. Extremely low birth weight infants born at 23 to 32 week's gestation with weight between 400 and 1000 g, followed up from birth to 36 weeks' postmenstrual age. Infants that died in the first 72 hours of life were excluded.

**Risk factor assessment:** exclusive human milk feeding during the period under study. The simulated cohort with an optimized feeding (OF) pattern consisted of 24 149 ELBW infants of who more than 90% received at least 98% of human milk (HM), compared to a simulated cohort of ELBW infants

with suboptimal feeding (SOF) patterns: some were exclusively fed preterm formula (PF) and the rest a mixed diet (MD). The model did not consider infants fed with donor human milk.

**Outcome assessment:** the primary outcomes were the incidence of necrotising enterocolitis (NEC) Bell stage II or higher, and death. The actual feeding pattern of each ELBW infant during the period under study was estimated using the weekly percentages reported in a previous retrospective single-centre study ( $n = 285$ )<sup>1</sup> and the multicentre Glutamine Trial (GT)<sup>2</sup> dataset ( $n = 1433$ ). The probability of developing NEC with the corresponding 95% confidence intervals (95 CIs) was estimated based on a subset of 848 infants through logistic regression modelling, obtaining adjusted odds ratios (aORs). Mortality due to NEC was estimated using rates from the Vermont Oxford Network (VON). The secondary outcome was reduction in costs based on Medicaid and Medicare data (increasing hospital hosts by 15% and adding the fees of neonatologists). The direct and indirect marginal costs were estimated adjusting for inflation and expressed in 2014 US dollars (US\$).

**Main results:** the GT analysis found that 9% of infants had an OF pattern and the rest a SOF pattern (MD in 67.5% and PF in 22.4%). The incidence of NEC was 1.3% for OF, 11.1% for MD and 8.2% for PF ( $P < .002$ ). The adjusted regression models showed an increased risk of NEC in infants fed a MD (aOR, 8.7; 95 CI, 8.7 to 65.2) or PF (aOR: 12.1; 95 CI, 1.5 to 94.2) compared to infants with an OF pattern. The study found no significant differences between infants with a MD and infants fed PF (aOR, 1.39; 95 CI, 0.83 to 2.33).

In the MCMC simulation, there was an annual excess of 928 cases of NEC (95 CI, 830 to 1036) and 121 deaths (95 CI, 108 to 134; 51% higher). The annual excess cost associated with SOF was 27.1 million US\$ (95 CI, 24 to 30.4) in direct costs and 563 655 US\$ (95 CI, 476 191 to 599 069) in indirect costs. The annual cost attributable to premature deaths due to NEC was 1.5 thousand million US\$ (95 CI, 1.3 to 1.6).

**Conclusion:** in ELBW infants, exclusive human milk feeding is associated with a lower risk of NEC and death due to NEC, and lower medical costs.

**Conflicts of interest:** none noted.

**Funding source:** none noted.

## COMMENTARY

**Justification:** necrotizing enterocolitis in ELBW infants is a major health problem in NICUs due to its high incidence (11.5%)<sup>3</sup> and associated morbidity and mortality. Previous

studies have found evidence that exclusive human milk feeding reduces both the incidence of NEC and its associated mortality,<sup>4</sup> but few studies have studied associated costs, which is why we believe that this study is pertinent.

**Validity/scientific rigour:** this is a cost-effectiveness study where the MCMC model seems to have been set up correctly and probabilities were estimated using data from scientific evidence of the highest quality. The duration of the study was appropriate (one year) and the additional effort to calculate weekly cycles is a strength. However, the perspective of the study is medical, not social, and the costs of the two compared options were not sufficiently defined. The costs (medical, direct and indirect) of the SOF option were exhaustively and rigorously calculated, but the study did not calculate the costs involved in the full implementation of OF: there was no estimation of the costs of promoting HM feeding or maintaining human milk banks in every hospital. The social costs (maternal leaves etc) were not included. All of the above would most likely increase the cost of the OF option. Therefore, the results are probably biased in favour of exclusive human milk feeding, as the authors acknowledged. Sensitivity analysis was not performed, and the analysis would have increased in rigour if the authors had performed a sensitivity analysis based on the percentage of infants fed with human milk and the human milk content of the diet. The benefits and costs of the two options were not rigorously compared. The final outcome was not expressed in marginal terms (marginal cost of prevented NEC cases or deaths due to NEC, cost by QALY or DALY) nor in exclusively monetary terms.

**Clinical relevance:** ELBW infants fed a MD were nine times more likely to develop NEC (aOR, 8.7; 95 CI, 8.7 to 65.2) with 928 excess NEC cases and 121 excess deaths in the SOF group. The relevance of these outcomes is diminished by their inaccuracy (wide confidence interval) and the limitations inherent in the study design. An observational study of associated costs found similar outcomes, with a reduction 3.9 days in NICU length of stay and of \$8167 in costs in ELBW infants exclusively fed human milk compared to infants fed artificial formula.<sup>5</sup>

**Applicability to clinical practice:** based on these findings, exclusive human milk feeding in ELBW infants would reduce the incidence of NEC and its associated mortality, as well as medical costs. The relevance of these results is lessened by the weaknesses of the study design. Although these findings add to the evidence that supports the promotion of human milk feeding, given the challenges involved in exclusive human milk feeding in everyday life, the actual economic efficiency of this approach in ELBW infants remains to be determined.

**Conflicts of interest:** the authors of the commentary have no conflicts of interest to declare.

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