Human Milk- vs. Cow Milk-Derived Fortification and Necrotizing Enterocolitis in Very Low Birthweight Infants: State of Evidence and Systematic Review With Meta-Analysis

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Objectives and Study

Necrotizing enterocolitis (NEC) remains a leading cause of morbidity and mortality in very low birth weight (VLBW) infants. While human milk feeding reduces NEC risk, evidence comparing human milk-derived versus cow milk-derived fortifiers remains mixed. We aimed to systematically evaluate the effects of an exclusive human milk diet (EHMD) with added vat-pasteurized human milk-derived fortifiers versus a cow milk-derived (CMD) diet utilizing cow milk-derived fortifiers on medical and surgical necrotizing enterocolitis in VLBW infants.

Methods

- Systematic review with meta-analyses conducted following PRISMA guidelines and registered on OSF
- Trials assessed for risk of bias, heterogeneity
- Included RCT or observational cohort study that investigated EHMD vs CMD and NEC in premature infants ≤1250 grams.
- Control group received cow milk-derived fortifiers or formula
- CMD further divided into with and without use of formula (CMD+f, CMD-f)
- CMD-f received base diet of human milk with cow milk-derived fortifiers
- Primary outcomes were medical and surgical NEC.

Results

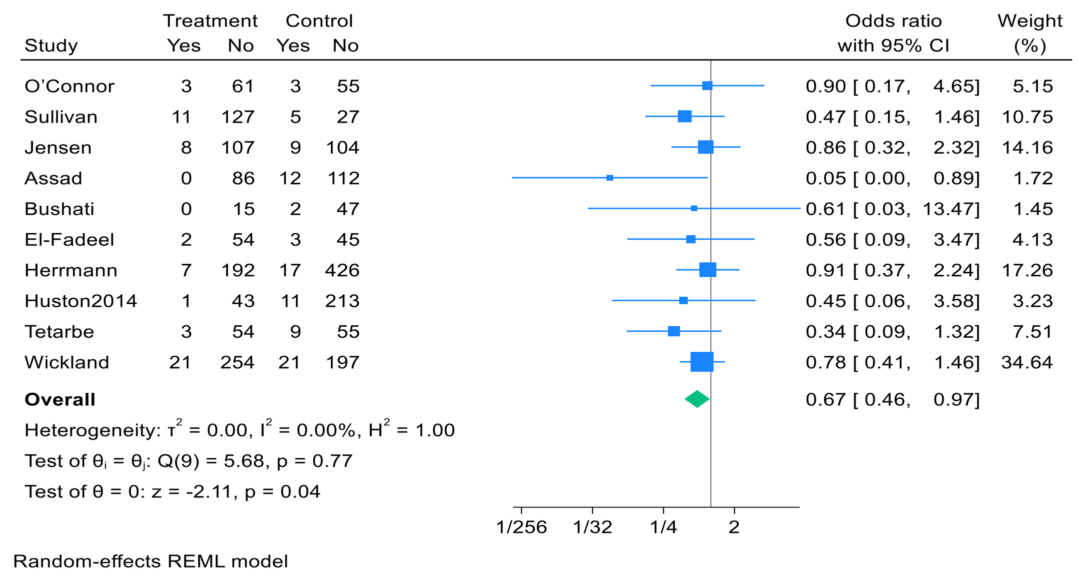
- Included 6 RCTs and 16 observational cohort studies
- Total Infants: 7,081; 3,258 on EHMD and 3,823 on CMD
- Birthweight 796 to 1361 gm, GA 25.5 to 29.8
- 13 studies reported any medical NEC; 11 reported Bells Stage ≥2 (3 RCTs, 8 observational); 6 reported surgical NEC (2 RCTs, 4 observational).
- Head-to-head comparisons of fortifiers EHMD vs. CMD-f:
  - EHMD 31% reduction in odds for Bells Stage ≥2 OR: 0.69, 95% CI, 0.48, 0.99; P=0.04; n=2,512) and
  - EHMD 50% reduction in surgical NEC (OR: 0.50, 95% CI, 0.26, 0.94; P=0.03; n=1,715).
- A similar effect size was seen for RCTs and observational studies for all comparisons.

Overall Summary of NEC Results
By Diet and Study Type

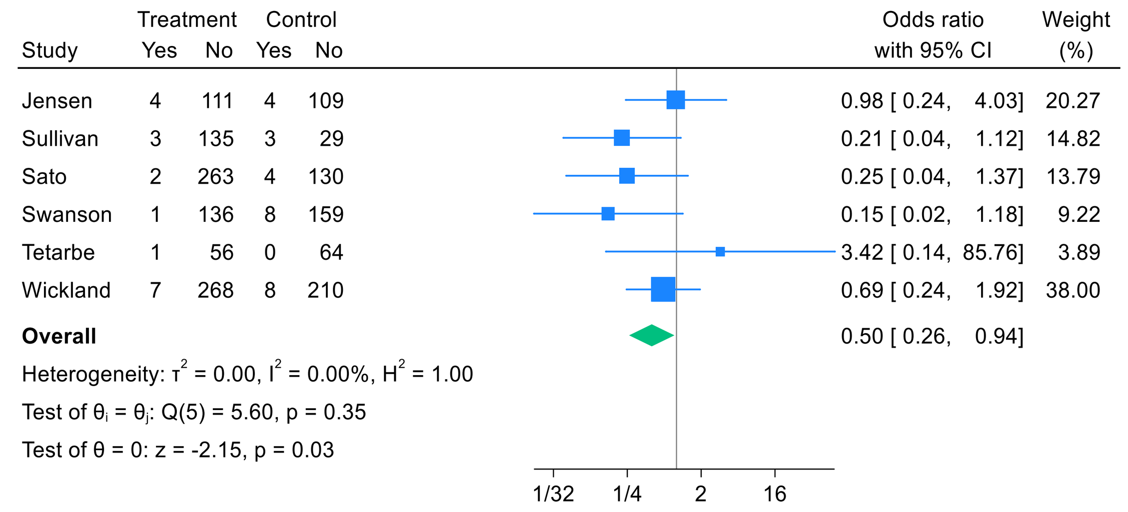
NEC type	EHMD vs. CMD+F			EHMD vs CMD-F		
	All Studies	RCT	Observational	All Studies	RCT	Observational
Bell Stage ≥2	41% ↓ 0.59 (0.43, 0.80) P = 0.0006 n = 5,073	32% ↓ 0.68 (0.37, 1.25) P = 0.21 n = 610	42% ↓ 0.58 (0.40, 0.85) P = 0.0001 n = 4,463	31% ↓ 0.69 (0.48, 0.99) P = 0.04 n = 2,512	30% ↓ 0.70 (0.35, 1.38) P = 0.30 n = 520	32% ↓ 0.68 (0.44, 1.05) P = 0.08 n = 1,992
Surgical NEC	56% ↓ 0.44 (0.31, 0.61) P < 0.0001 n = 4,591	53% ↓ 0.47 (0.20, 1.12) P = 0.09 n = 651	56% ↓ 0.60 (0.44, 0.81) P = 0.001 n = 3,940	50% ↓ 0.50 (0.26, 0.94) P = 0.03 n = 1,715	51% ↓ 0.49 (0.11, 2.16) P = 0.34 n = 398	52% ↓ 0.48 (0.21, 1.11) P = 0.08 n = 1,317

Results

Medical NEC Bell's Stage ≥2: EHMD vs cow milk-derived fortifiers with base diet of human milk
N=2,512



Forest plots were generated using logistic mixed effects models—CI, confidence interval; CMD-F, cow milk fortifiers added to human milk; EHMD, exclusive human milk diet; NEC, necrotizing enterocolitis.



Surgical NEC: EHMD vs cow milk-derived fortifiers with base diet of human milk
N=1,715

Forest plots were generated using logistic mixed effects models—CI, confidence interval; CMD-F, cow milk fortifiers added to human milk; EHMD, exclusive human milk diet; NEC, necrotizing enterocolitis.

Conclusions

EHMD reduced risk of medical and surgical NEC in VLBW infants ≤1,250 g. With a base diet of human milk, vat-pasteurized human-derived fortifiers reduced NEC when compared to cow milk-derived fortifiers. The odds of medical NEC were reduced by ~30% and the odds of surgical NEC reduced by ~50%. The effect was similar across study types despite different p values. The consistency of effect sizes across study types suggests clinically meaningful benefits, though standardization of fortification protocols and feeding practices is needed in future research.