

Towards a NEC free NICU: *Prevention of Necrotising Enterocolitis*

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NEC: Burden of disease

- Incidence (\geq Stage II) in VLBWS: 7-10%
- Mortality 15 – 30%
- Morbidity
 - Surgery(Perforation) 20 – 40%
 - Wound complications
 - Intra-abdominal abscess
 - Intestinal strictures
 - Short bowel syndrome
 - Prolonged TPN
 - Prolonged hospital and NICU stay
 - Adverse neurodevelopmental outcome



Prevention of NEC in the VLBW infant

- What is the evidence for different feeding strategies in the prevention of NEC?
- Is there a place for the routine use of probiotics in NEC prevention?
- What evidence is there for other interventions in preventing NEC?

Feeding Practices and NEC: Current Evidence

- Human milk(MOM) decreases NEC incidence (Observational studies)
 - 3-10 times incidence of NEC in formula fed prems
 - Dose-dependent effect: >80% protection if comprises >50% feeds for 14 days
- Human milk(Donor) vs formula significantly reduces the risk of NEC
 - Formula increases risk of NEC by 2,8 times. NNH= 17

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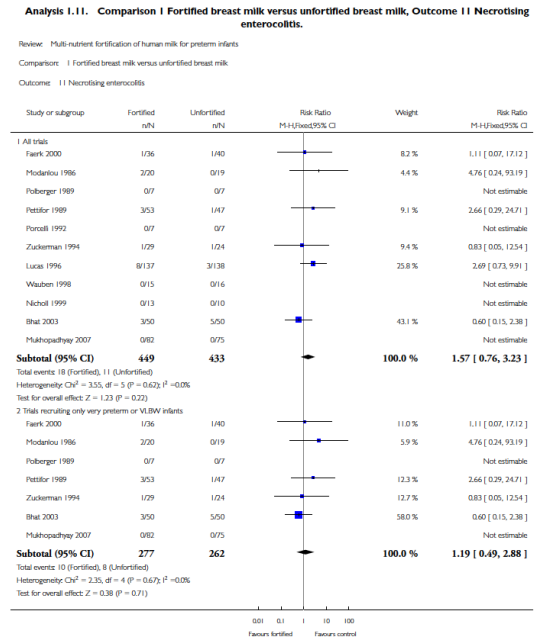


Human milk is the feeding strategy to prevent necrotizing enterocolitis!



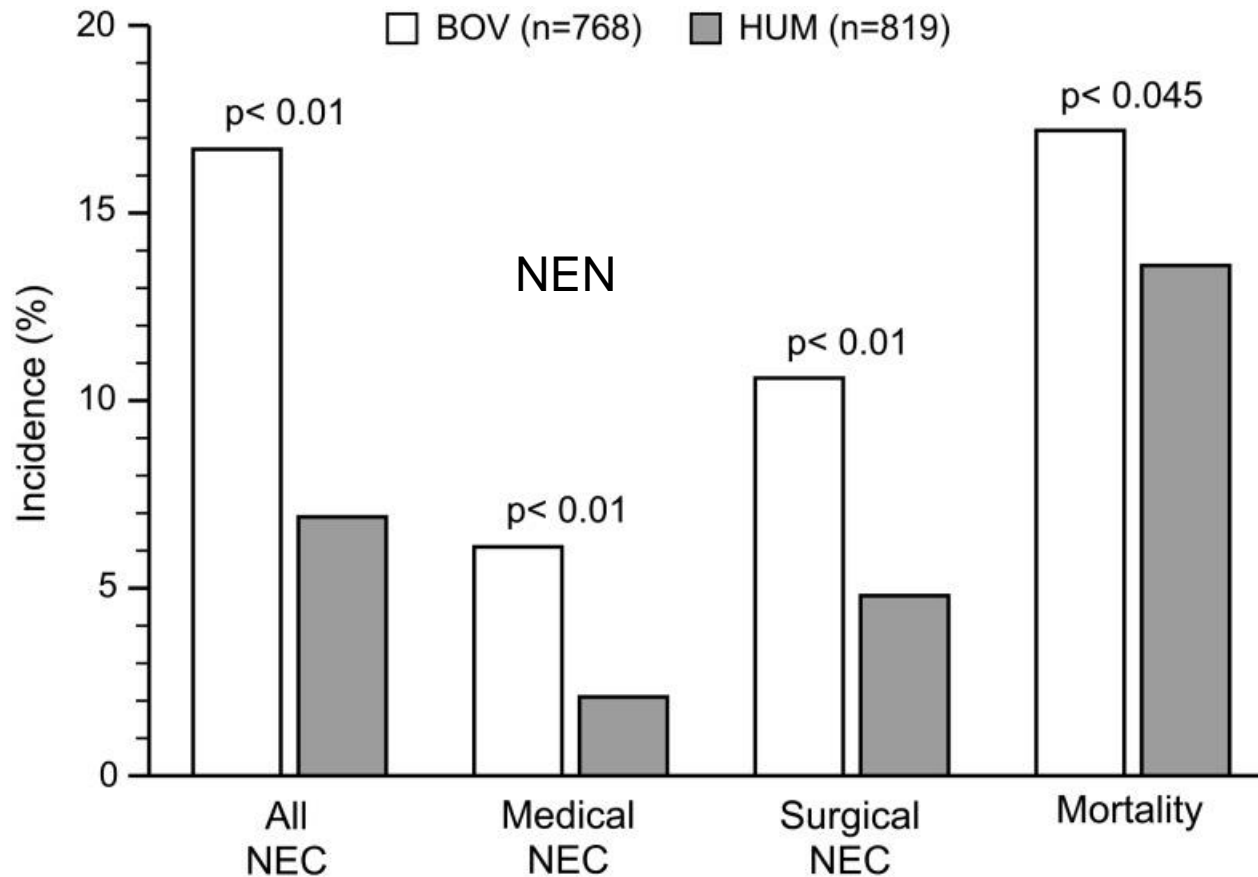
Feeding Practices and NEC: *Current Evidence*

- Multinutrient fortification of human milk (bovine/human/preterm formula)
 - Low quality evidence (GRADE)
 - Increased in-hospital growth
 - Limited data for growth and development beyond infancy: No effects
 - Fortification does not increase risk of NEC



(Continued...)

Beyond NEC Prevention: Improving Outcomes with an Exclusive Human Milk-based Diet



- MEN (Trophic feeding) does not increase the risk of NEC. Fasting does not protect against NEC.
- In stable VLBWs advancement of feeds at a slower rate (15-20mL/kg/d) vs faster rate (20-25mL/kg/d) does not reduce the risk of NEC/death.
Delay in establishing full feeds; increased sepsis
- There is no evidence supporting continuous or intermittent feeds
- In feeding intolerance with no other clinical evidence of NEC, MEN with frequent monitoring may be an alternative to complete suspension of feeds.

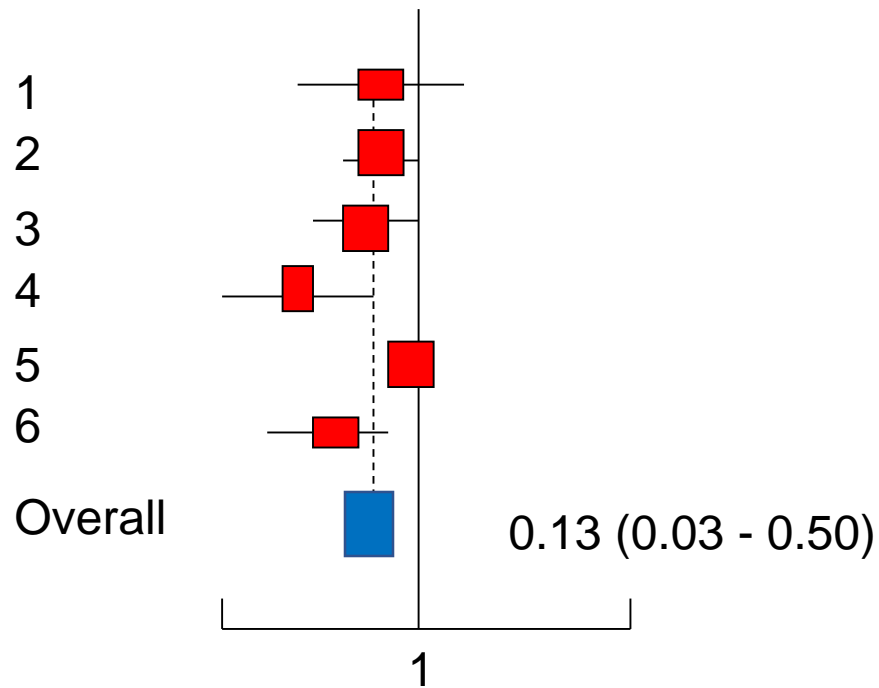
ORIGINAL ARTICLE

Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies

S K Patole, N de Klerk

Arch Dis Child Fetal Neonatal Ed 2005;**90**:F147–F151. doi: 10.1136/adc.2004.059741

RR (95% CI)



Impact of Standardised Feeding Regimens on Incidence of NEC
Patole and de Klerk *Arch Dis Child* (2005)

EDITORIAL

Probiotics for Preterm Infants – The Story Searching for an End

Impact of probiotics on NEC: RCTs and Cohort studies

Type of study	N	Probiotic vs Placebo		NEC (%)		Sepsis (%)		Death (%)	
		Prob	Plac	Prob	Plac	Prob	Plac	Prob	Plac
RCT	35	5559	5513	3.3	6.1	12	14	5.1	7.2
Cohort	11	7742	7592	1.4	4.4	12	14	7.6	9.2

<i>Prob- probiotic</i>	<i>Plac- placebo</i>
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Underwood MA. *Seminars in Perinatology*. 2017; 41:41-51.

Impact of probiotics on NEC: Meta-analyses

Study	Year	No of studies	NEC RR (95% CI)	Death RR (95% CI)
Billimoria	2016	30	0.55(0.45-0.66)	0.72(0.60-0.87)
Olsen	2016	12	0.55(0.39-0.78)	0.72(0.61-0.85)
Aceti	2015	26	0.47(0.36-0.60)	
Aggarwal	2015	23		0.69(0.56-0.86)
Lau	2015	20	0.51(0.39-0.67)	0.73(0.58-0.93)
Athalye-Jape	2016	8	0.69(0.47-1.01)	0.79(0.57-1.09)
Al Faleh <i>Cochrane</i>	2014	24	0.43(0.33-0.56)	0.65(0.52-0.81)

Underwood MA. *Seminars in Perinatology*. 2017; 41:41-51

Billimoria ZC et al. *Clinical Pediatrics*. 2016; 55(13):1242-1244

- ***Routine prophylactic probiotics is the 'most studied, safe and effective intervention ever to be rejected by US neonatology'similar to the delay in introducing resuscitation with room air.***
- ***USA:-***
 - ***3000 NEC cases per year (5% of <1500 g birth weight)***
 - ***600 deaths per year (20% Mortality)***
- ***Probiotics- RR reduction of 0.5***
 - ***Estimated savings per year of increased probiotic use:***
 - ***Lives 300***
 - ***Meters of intestines 120***
 - ***Millions of dollars 250***
 - ***Billions of neurones 12,000***

Reasons for not using probiotics to prevent NEC

- Risks
 - Sepsis due to administered probiotic.
 - Contamination of available probiotic with pathogens (Quality)
 - Failure of preparation to contain numbers/strains as indicated (Viability)
 - Cross-contamination (49%)
 - Call for large cluster or cross-over cluster RCTs-
Randomize ICUs
 - Probiotics be registered as pharmaceuticals and not food additives (Quality and Viability)
- Evidence- low quality, not rigorous, heterogeneity in meta-analyses
- Which probiotic/dosage/duration?
 - Studies not powered to detect differences in NEC incidence
 - Combination products probably preferable

PiPPS trial	<i>B breve</i> n=650 %	Placebo n=660 %	RR (95% CI)
NEC	9	10	0.93(0.68-1.27)
Sepsis	11	12	0.97(0.73-1.29)
Death	8	9	0.93(0.67-1.30)

49% Cross contamination.

Costeloe K et al. *Lancet* 2016; 387:649-660

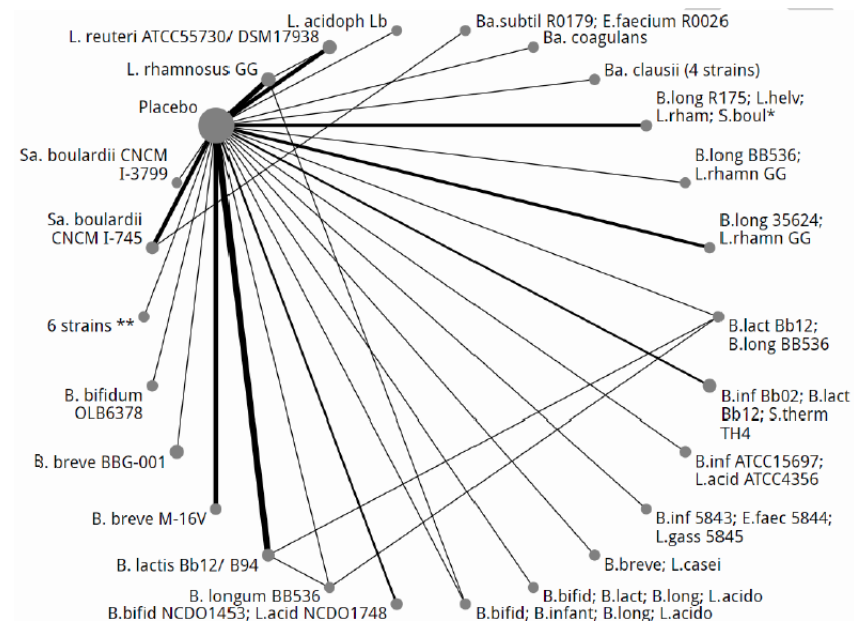
ProPrem trial	<i>B infantis</i> <i>B lactis</i> <i>St thermophilus</i> n=548 (%)	Placebo n=551 (%)	RR (95% CI)
NEC	2	4	0.46(0.23-0.93)
Sepsis	13.1	16.2	0.81(0.61-1.08)
Death	4.9	5.1	0.97(0.58-1.62)

*ABC Dophilus withdrawn - contamination with Rhizopus oryzae
Fatal mucomycosis in prems given ABC Dophilus*

Jacobs SE et al. *Pediatrics* 2013;(132):1055-1062

Probiotics for Preterm Infants: a strain specific systematic review and network meta-analysis (NMA)

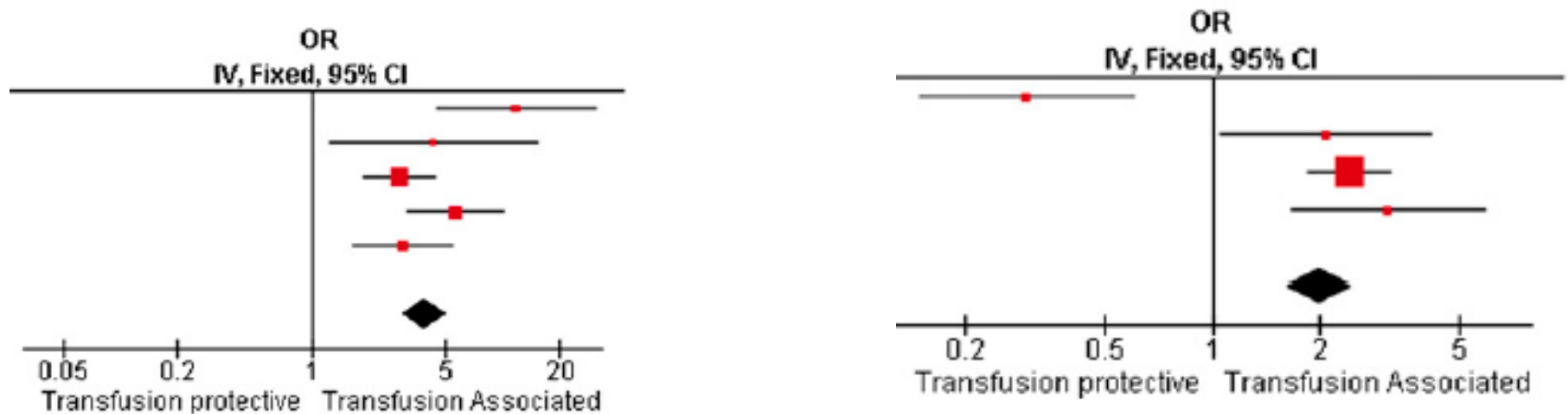
- 51 RCTs involving 11,231 preterm infants
- Placebo-controlled or head-to-head RCTs
- Efficacy in reducing NEC, LOS, TUEEF, mortality only in a minority of strains or combinations
- May be due to inadequate sample number or true lack of effect for different strains or combinations



EDITORIAL

Probiotics for Preterm Infants – The Story Searching for an End

Transfusion Associated Necrotizing Enterocolitis: A Meta-analysis of Observational Data



Unadjusted and adjusted estimates of exposure to transfusion among NEC versus no NEC patients.

Transfusion-associated necrotizing enterocolitis in preterm infants: an updated meta-analysis of observational data

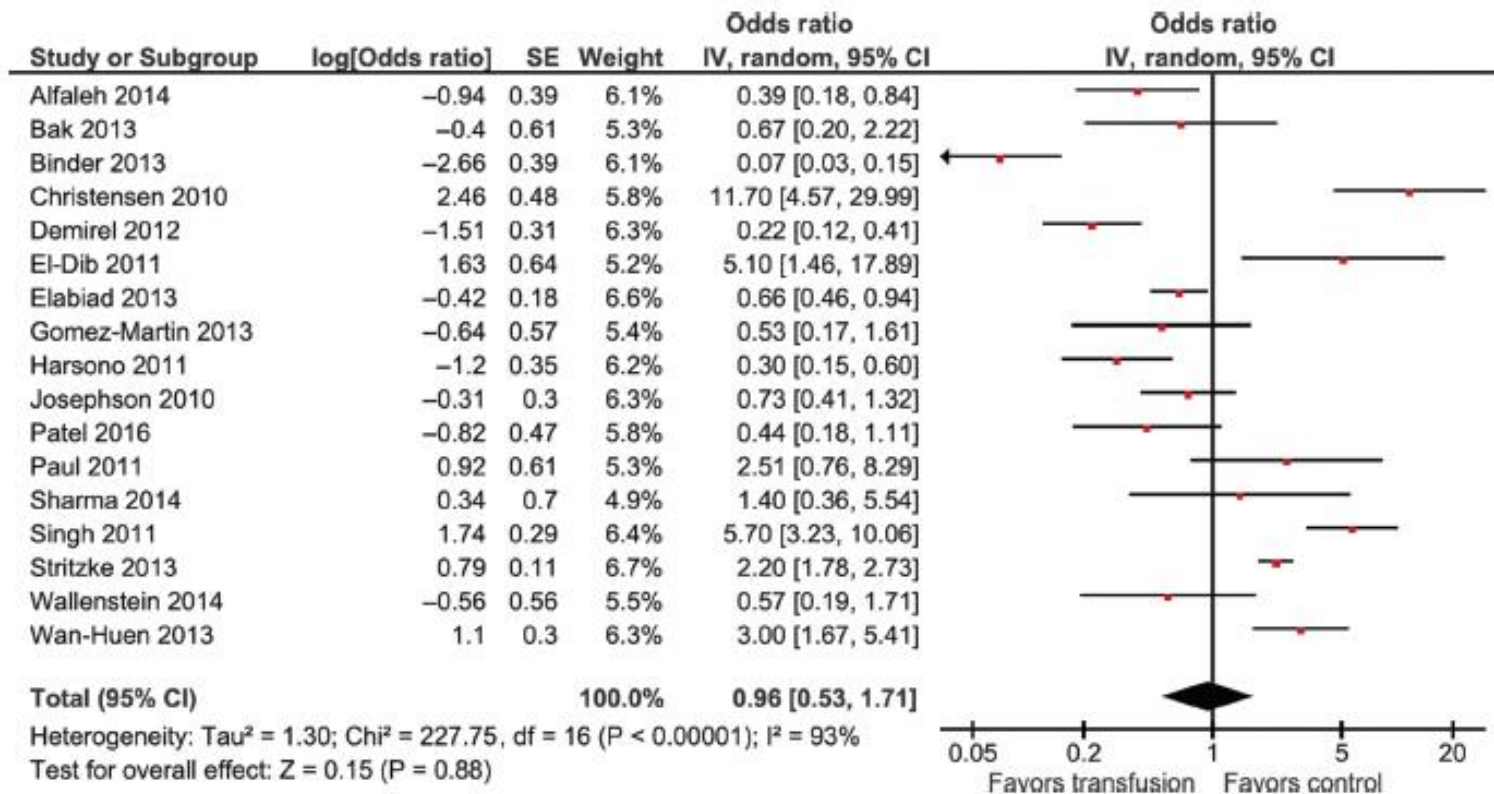


Figure 1: Meta-analysis of studies included.

Other strategies

- **Antenatal steroids**
 - NEC reduced by 54%
- **Delayed cord clamping**
 - NEC reduced by 40%
 - NNT 12
- **Avoid H2 Blockers**
 - 70% increased risk of NEC
 - Effective, recommended
- **Avoid prolonged (>5days) empirical antibiotic use**
 - 61% vs 51%
 - 3X increase in NEC
 - Effective, recommended

Other strategies

- **Oral immunoglobulins**

- Not effective

- **Lactoferrin**

- NEC decreased (low quality evidence)
- Large clinical trial underway
- Not recommended

- **Arginine**

- May be protective
- Data inadequate
- Not recommended

- **Glutamine**

- Not effective

- **Human milk- oligosaccharides**

- May be protective

- **Polyunsaturated fatty acids**

- May be protective

- **Erythropoietin**

- May be protective

- **Acetylhydrolase**

- May be protective

Take home messages.....

- Human milk is the single most important protective factor.
- Early feeding does not increase the risk of NEC.
- Fortifiers not associated with increased risk of NEC.
- Cautious approach in advancement of feeds and management of feeding intolerance is justified as part of standardized feeding regimens.
- No place for the routine use of probiotics. (?)
- Transfusions not associated with NEC, but anaemia is.
- Further studies needed on other, newer interventions.
- Pathogenesis of NEC (Role of the intestinal microbiome) needs further study.
- Techniques for more accurate, early diagnosis need further study.