Dr. Sampath is a physician-scientist and Neonatology. He loves clinical care, mentoring/education and is big-time into research. Outside work he likes the outdoors, philosophy, and music.
Feeding strategies to prevent NEC
- The current and future

Venkatesh Sampath, MBBS, MRCPCh
Professor of Pediatrics/Neonatology
Sosland Endowed Chair in Neonatal Research
Children's Mercy Hospital

No financial or other conflicts.
Personal Biases are disclosed
Disclosure

No financial or other conflicts to disclose.

Recommendations that are not evidence-based are disclosed.

Will limit mouse data to minimum.
NEC pathogenesis - Current Understanding

Berdon et al. Radiology 1964 PMID: 14229131

Mucosal Ischemia
Aberrant colonization
? Genetic Factors
Immature immune system

Mucosa

TLR

TLR4

TLR

TLR

TLR4

NEC

Inflammation

Necrosis

SIRS

Immune cells

Lymphocytes

Tissue sample

Radiographs

LOVE WILL.
NEC - Feeding practices (Breast milk protects)


**TABLE III—NECROTIZING ENTEROCOLITIS BY FEED GROUP**

<table>
<thead>
<tr>
<th>Feed Group</th>
<th>No (%) of cases</th>
<th>All cases</th>
<th>Confirmed cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula only</td>
<td>236</td>
<td>24 (10.2%)</td>
<td>17 (7.2%)</td>
</tr>
<tr>
<td>Formula plus mother’s milk</td>
<td>437</td>
<td>16 (3.7%)</td>
<td>11 (2.5%)</td>
</tr>
<tr>
<td>Human milk only</td>
<td>253</td>
<td>11 (4.3%)</td>
<td>3 (1.2%)</td>
</tr>
</tbody>
</table>

**Gestation**

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Formula only</th>
<th>Human milk*</th>
<th>Confirmed cases</th>
<th>Formula only</th>
<th>Human milk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–27 wk</td>
<td>7/35 (20%)</td>
<td>13/83 (16%)</td>
<td>5/35 (14%)</td>
<td>7/83 (8%)</td>
<td></td>
</tr>
<tr>
<td>28–30 wk</td>
<td>7/83 (8%)</td>
<td>11/231 (5%)</td>
<td>5/83 (6%)</td>
<td>6/231 (3%)</td>
<td></td>
</tr>
<tr>
<td>31–33 wk</td>
<td>6/75 (8%)</td>
<td>3/263 (1%)</td>
<td>3/75 (4%)</td>
<td>1/263 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>34–36 wk</td>
<td>4/43 (9%)</td>
<td>0/113</td>
<td>4/43 (9%)</td>
<td>0/113</td>
<td></td>
</tr>
</tbody>
</table>
Is there a benefit of partial human milk intake?

- Exclusive Human Milk vs. Exclusive preterm formula (Observational) - 3 trials; NEC - 6/555 infants vs. 24/438 infants. Risk ratio - 0.22 (0.09 - 0.54). **YAY!**

- Any human milk use vs. Exclusive preterm formula (Observational) - 9 studies; NEC – 102/2938 vs. 62/845 infants. Risk ratio - 0.51 (0.34 - 0.76). **YAY!**

- Higher vs. lower human milk intake (Randomized control trials) - 4 studies; NEC – 33/583 vs. 50/533. Risk ratio – 0.54 (0.28 – 1.02). **ALMOST YAY!**

- Higher vs. lower human milk intake (Observational) - >20 studies; NEC – 204/4242 vs. 363/4536. Risk ratio – 0.53 (0.42 – 0.67). **YAY!**

- **Take home:** Breast milk better; Some (>40-50ml/kg/day) brings good benefit

Miller et al. Nutrients 2018; PMID: 29857555
NEC: Donor EBM vs. Preterm formula

- 12 trials (1870 infants): 4 trials Term vs. Donor EBM; 8 Preterm Formula vs. Donor EBM. Only 5 trials fortified Donor EBM vs. preterm formula.

- Most studies sponsored by Preterm formula companies; Blinding infrequent; Allocation bias 6 trials.

- Formula-fed infants: Higher rate of weight gain (Mean difference 2.51, 95% CI 1.93 to 3.08 g/kg/day; 9 trials, N =1028; moderate-certainty evidence;)

- Significant subgroup differences existed with the largest effect size for the comparison of preterm formula with unfortified donor breast milk (MD 4.16, 95% CI 3.04 to 5.28 g/kg/day).

Cochrane Database Syst Rev. 2019 Jul 19;7:CD002971. Quigley M¹, Embleton ND, McGuire W.
Donor EBM vs. Preterm formula – NEC rates

### Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.25.1 Term formula versus unfortified DBM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grooss 1983</td>
<td>3</td>
<td>26</td>
<td>1</td>
<td>2.5%</td>
<td>4.73 (0.52, 43.09) 1983</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>41</td>
<td>41</td>
<td>1</td>
<td>2.5%</td>
<td>4.73 (0.52, 43.09) 1983</td>
</tr>
<tr>
<td>Total events</td>
<td>41</td>
<td>41</td>
<td>1</td>
<td>2.5%</td>
<td>4.73 (0.52, 43.09) 1983</td>
</tr>
<tr>
<td>Heterogeneity: N/A test for overall effect: Z = 1.39 (p = 0.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 1.25.2 Preterm formula versus unfortified DBM

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyson 1983</td>
<td>1</td>
<td>44</td>
<td>0</td>
<td>1.0%</td>
<td>2.53 (0.11, 66.39) 1983</td>
</tr>
<tr>
<td>Lucas 1984a</td>
<td>4</td>
<td>76</td>
<td>1</td>
<td>3.1%</td>
<td>4.37 (0.50, 36.23) 1984</td>
</tr>
<tr>
<td>Lucas 1984b</td>
<td>5</td>
<td>172</td>
<td>2</td>
<td>6.5%</td>
<td>2.49 (0.48, 12.49) 1984</td>
</tr>
<tr>
<td>Costa 2013</td>
<td>0</td>
<td>35</td>
<td>0</td>
<td></td>
<td>Not estimable 2018</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>328</td>
<td>325</td>
<td>11.4%</td>
<td>2.99 (0.90, 9.87)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>328</td>
<td>325</td>
<td>11.4%</td>
<td>2.99 (0.90, 9.87)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² (df = 2) (p = 0.01), p = 0% test for overall effect: Z = 1.93 (p = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 1.25.3 Preterm formula versus fortified DBM

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schaner 2005</td>
<td>10</td>
<td>108</td>
<td>5</td>
<td>17.2%</td>
<td>1.77 (0.63, 4.98) 2005</td>
</tr>
<tr>
<td>Cristales 2013</td>
<td>5</td>
<td>24</td>
<td>1</td>
<td>2.9%</td>
<td>6.04 (0.76, 46.29) 2013</td>
</tr>
<tr>
<td>O'Connor 2016</td>
<td>12</td>
<td>102</td>
<td>3</td>
<td>9.8%</td>
<td>3.90 (1.14, 13.86) 2016</td>
</tr>
<tr>
<td>Carroll 2016</td>
<td>17</td>
<td>100</td>
<td>17</td>
<td>66.2%</td>
<td>0.68 (0.51, 1.33) 2016</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>484</td>
<td>471</td>
<td>86.6%</td>
<td>1.64 (1.04, 2.61)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>44</td>
<td>46</td>
<td>26</td>
<td>2.9%</td>
<td>6.04 (0.76, 46.29) 2013</td>
</tr>
<tr>
<td>Heterogeneity: Ch² (df = 3) (p = 0.11), p = 61% test for overall effect: Z = 2.90 (p = 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### All cause mortality was no different between groups

Cochrane Database Syst Rev. 2019 Jul 19;7:CD002971. Quigley M¹, Embleton ND, McGuire W.
## Donor EBM vs. Preterm formula – Linear Growth

**Crown Heel Length mm/wk**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Formula milk</th>
<th>Donor breast milk</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.3.1 Term formula versus unfortified EBM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davies 1997</td>
<td>9.3</td>
<td>2</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Gross 1993</td>
<td>7.2</td>
<td>1</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>74</td>
<td>40.2%</td>
<td>0.00 (0.10, 1.50)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: CHI² = 0.00, df = 1 (P = 1.00); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.25 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **1.3.2 Preterm formula versus unfortified EBM** |
| Lucich 1984a      | 9.7          | 2.2               | 12                                |              |
| Lucich 1984b      | 9.6          | 2.2               | 20                                |              |
| Subtotal (95% CI) | 73           | 26.6%             | 1.96 (1.10, 2.82)                 |              |
| Heterogeneity: CHI² = 5.77, df = 2 (P = 0.06); I² = 65% |
| Test for overall effect: Z = 4.49 (P = 0.00001) |

| **1.3.3 Preterm formula versus fortified EBM** |
| Christoffo 2013   | 11.2         | 2.9               | 24                                |              |
| O'Connor 2013     | 10.7         | 4.6               | 162                               |              |
| Schanler 2005     | 10           | 10                | 88                                |              |
| Subtotal (95% CI) | 274          | 33.2%             | 1.10 (0.33, 1.87)                 |              |
| Heterogeneity: CHI² = 11.93, df = 2 (P = 0.003); I² = 69% |
| Test for overall effect: Z = 2.81 (P = 0.005) |

**Total (95% CI)** |

| 402               | 418          | 100.0%            | 1.21 [0.77, 1.65]                |
|                  |              |                   |                                   |

<table>
<thead>
<tr>
<th>Risk of bias legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Random sequence generation (selection bias)</td>
</tr>
<tr>
<td>(B) Allocation concealment (selection bias)</td>
</tr>
<tr>
<td>(C) Blinding (performance bias and detection bias)</td>
</tr>
<tr>
<td>(D) Incomplete outcome data (attrition bias)</td>
</tr>
<tr>
<td>(E) Selective reporting (reporting bias)</td>
</tr>
<tr>
<td>(F) Other bias</td>
</tr>
</tbody>
</table>

Cochrane Database Syst Rev. 2019 Jul 19;7:CD002971. Quigley M¹, Embleton ND, McGuire W.
Donor EBM vs. Preterm formula – Head Growth


MD 0.85, 95% CI 0.47 to 1.23 mm/week; I² = 74%; 8 trials, 894 participants; moderate-certainty evidence
Donor Human Milk - “Yay” or “Nay”

- 18-month Developmental Outcomes in Donor vs. Formula – Less studied; No difference; One study; Trend towards worse outcomes with donor milk.
- No difference is all cause mortality between Donor vs. Formula milk.
- Decreased NEC with Donor EBM (40%) but worse short-term growth outcomes, CMV is also concern; 18-month neurological outcomes unclear.
- In premies receiving > 60mL/kg/day of MOM, Donor EBM does not confer additional NEC benefits (Schanler 2005; Others). If no access to DONOR milk, then even some MOM + formula milk might be ok.
- Three other clinical trials (US and international) ongoing.
Feed intolerance/potential NEC – Careful about Feed Osmolality

  - Tested osmolality of fortified feeds with supplements/drugs.

- ~400mOsm/L is recommended; EBM is 300: most formulas are <450. Additives and drugs can markedly increase osmolality.

- 6 RCTs; 4 compared routine pre-feed aspirate checking to no checking.
Bolus vs. continuous feeds in VLBW infants

- Bolus feeds more “physiological” or is it? Baby vs. “fetus”
  Continuous vs. Bolus feeds infants < 1500g. Premji SS, Chessell L (Cochran 2011)
  ➢ 7 trials, (n=511 infants), b.wt 500-1500g.
  ➢ No difference for time to full feeds or NEC rates.
  ➢ One study showed trend towards more apneas with bolus feeds.
  ➢ One study- sub-group analysis; Infants <1000g had better weight gain on continuous feeds, earlier discharge to home.


**Conclusion:** It’s a wash, bias towards continuous feeds in ELBW babies.
Does advancing feeds slowly prevent NEC?

14 RCTs. N=4033 infants (2804 - one large trial). 33% were ELBW infants.


<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with faster rates of enteral feed advancement</td>
<td>Risk with slow rates of enteral feed enhancement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrotising enterocolitis before hospital discharge</td>
<td>54 per 1000</td>
<td>57 per 1000 (45 to 77)</td>
<td>RR 1.06 (0.83 to 1.37)</td>
<td>4026 (14 trials)</td>
</tr>
<tr>
<td>Mortality before hospital discharge</td>
<td>71 per 1000</td>
<td>80 per 1000 (64 to 98)</td>
<td>RR 1.13 (0.91 to 1.39)</td>
<td>3860 (13 trials)</td>
</tr>
<tr>
<td>Feed intolerance before hospital discharge</td>
<td>282 per 1000</td>
<td>333 per 1000 (268 to 412)</td>
<td>RR 1.18 (0.95 to 1.46)</td>
<td>719 (9 trials)</td>
</tr>
<tr>
<td>Invasive infection before hospital discharge</td>
<td>170 per 1000</td>
<td>194 per 1000 (168 to 223)</td>
<td>RR 1.14 (0.99 to 1.31)</td>
<td>3583 (11 trials)</td>
</tr>
</tbody>
</table>
**Milk-Feeding Rates in Preterm Infants**

**MULTICENTER, PARALLEL-GROUP, RANDOMIZED, CONTROLLED TRIAL**

<table>
<thead>
<tr>
<th>Infants born at &lt;32 wk gestation or &lt;1500 g birth weight</th>
<th>Survival without moderate or severe neurodevelopmental disability at 24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2804</td>
<td>No significant between-group difference in confirmed or suspected late-onset sepsis or Bell's stage 2 or 3 necrotizing enterocolitis</td>
</tr>
</tbody>
</table>

### Daily Milk Increment

<table>
<thead>
<tr>
<th>30 ml/kg (N = 1224)</th>
<th>18 ml/kg (N = 1246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65.5%</td>
<td>68.1%</td>
</tr>
</tbody>
</table>

Adjusted RR, 0.96; 95% CI, 0.92–1.01

SIFT trial
Death+mod-severe developmental impairment at 24 month CGA – No difference
Transfusion associated NEC happens in chronically anemic preterm infants 48 hr after transfusion. Usually ELBW infants, can be quite severe.

45 studies, narrowed it down to 26 studies (23 observational, 3 RCT).

Overall quality of studies “low” to “very low”. RCTs- NEC not primary outcome.

TANEC (<48hr) - 1.13 (0.99–1.29), NEC anytime after PRBCs (1.95 (1.6–2.4)], From RCT (n=3), NEC was lower with liberal transfusion [0.6 (0.3 – 1.21)].

A) Major bias – unadjusted for co-variates; potential for confounding for indication. Example – apnea – transfusion – NEC. B) Significant inconsistency among studies in trend of results; C) No specific definition of TRALI process.
TANEC - Impact of NPO before and after transfusion

➢ Holding feeds 4-6 hr before, during, and 4-6 hr after PRBC transfusion common.
➢ One very small RCT (N=22); no differences in Splanchnic blood flow or NEC.
➢ 7 studies which compared pre- and post policy change. (N=7492 infants)

Take home: Possibly safer to hold feeds for PRBC Rx (low quality of evidence)
Quick Takes

Can we feed infants during medical treatment of PDA? (Stage I or II)


How soon after medical NEC can we feed? 5d, 7d or forever? (Patel/Ryan et al.)

Take home: Early limited evidence - Can re-feed after medical NEC around 4-5 days.
Human Milk - Beyond Nutrition

Antibacterial factors

1. Lactoferrin
2. IgA

Pathogenic microbes

1. Klebsiella
2. E Coli
3. Pseudomonas

Trophic factors

1. Human milk
2. HMOs
3. Microbiome modulation

Gram-negative bacteria

Intestinal inflammation, injury and NEC

Adapted from Sampath et al. Mucosal Immunology March 2013
Probiotics and NEC: mechanisms

1. Improved barrier function (preventing bacteria from invading gut)
   1. Apoptosis
   2. Tight junctions
   3. Mucin production

2. Decreased inflammation by gene regulation
   1. Less TLR4, More SIGIRR, A20
   2. IL1-beta, IL6, TNF-alpha
   3. Tryptophan metabolites (Indole-3-lactic acid)

3. Alteration of the microbiota
   1. Bacteriocins
   2. Competition for nutrients (HMOs, Fe)

Yu Y, PLoSOne 2020
Meng D, Pediatr Res 2020
Halloran K, Early Hum Dev 2019
Cuna/Wei/Sampath 2020
# Probiotics and NEC: Observational Systematic review of non-RCTs using Cochrane methodology

Good-quality studies from 18 countries

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Preterm infants</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC stage 2 or 3</td>
<td>30</td>
<td>77,018</td>
<td>0.60 (0.50, 0.73)</td>
<td>&lt;0.00001</td>
<td>Moderate</td>
</tr>
<tr>
<td>LOS</td>
<td>21</td>
<td>65,858</td>
<td>0.85 (0.74, 0.97)</td>
<td>0.02</td>
<td>Low</td>
</tr>
<tr>
<td>Death</td>
<td>27</td>
<td>70,977</td>
<td>0.77 (0.68, 0.88)</td>
<td>0.0001</td>
<td>Low</td>
</tr>
</tbody>
</table>

ELBW: NEC stage >2: 4.5% (probiotic) vs 7.9% (no probiotic)
### Probiotics and NEC: RCTs

**Systematic review of RCTs using Cochrane methodology**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials</th>
<th>Preterm infants</th>
<th>RR (95% CI)</th>
<th>NNTB (95% CI)</th>
<th>Certainty of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC stage 2 or 3</td>
<td>54</td>
<td>10,604</td>
<td>0.54 (0.45, 0.65)</td>
<td>33 (25, 50)</td>
<td>Low</td>
</tr>
<tr>
<td>NEC stage 2 or 3 (low risk of bias)</td>
<td>16</td>
<td>4597</td>
<td>0.70 (0.55, 0.89)</td>
<td>50 (33, 100)</td>
<td>Moderate</td>
</tr>
<tr>
<td>LOS</td>
<td>47</td>
<td>9762</td>
<td>0.89 (0.82, 0.97)</td>
<td>50 (33, 100)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Death</td>
<td>51</td>
<td>10,170</td>
<td>0.76 (0.65, 0.89)</td>
<td>50 (50, 100)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Meta-analysis did not show effects on NEC, death, or infection for ELBW infants (low-certainty evidence)

---

Sharif S, Cochrane Database Sys Rev 2020

Courtesy of Dr. Mark Underwood  MD
Probiotics in preterm infants – Striking evidence

Probiotics - Drawbacks

➢ Sepsis from probiotics - Rare, Saccharomyces, Lactobacillus rhamnosus in preterm infants. Under reported ?; In RCTs, sepsis rate lower with probiotics. Contamination with pathogenic bacteria reported.

➢ Main issue; Which preparation; how many bacteria? IND vs.dietary supplement.

➢ Cross-contamination (49%) of placebo infants in trials get colonized.

➢ Which probiotics is best ?
  ❑ Combination generally better (Infloran – Bifidobacteria + Lactobacillus).
  ❑ Bifidobacteria > Lactobacillus > Saccharomyces.
  ❑ Underwood MA: parental consent trial appropriate ?? (best in US Florababy, L. rhamnsosus + Bifidobacteria 4 strains); Infloran (L.acidophilus B.infantis)
Lactoferrin


- Both human recombinant and bovine lactoferrin commercially available.

- No differences in NEC stage II or III (typical RR 1.10, 95% CI, 0.86 to 1.41; 7 studies, 4874 participants; low-certainty evidence).

- Confirmed late-onset sepsis (typical RR 0.83, 95% CI 0.73 to 0.94; typical RD -0.03, 95% CI, -0.04 to -0.01; NNTB 33, 12 studies, 5425 participants, low-certainty evidence).

- Combined with probiotics - NEC stage II or III (RR 0.04, 95% CI 0.00 to 0.62; NNTB 20, 95% CI 12.5 to 33.3; 1 study, 496 participants; very low-certainty evidence).

• Pammi et al. 2020 Cochrane Database PMID: 32232984, PMCID: PMC7106972
NEC prevention – Bacteria-free Prebiotics?

• 3rd most abundant component of human milk is?

• Human milk oligosaccharides - 10-15g/L of mother’s milk. Non absorbable carbohydrates not of direct nutritional value to babies.

• Favor growth of Good bacteria Bifidobacteria spp.

Ma et al. *Nutrients* 2022, 14(23), 5148; [https://doi.org/10.3390/nu14235148](https://doi.org/10.3390/nu14235148)
NEC prevention – Bacteria-free Prebiotics ?

➢ 18 RCTs; N=1322 infants

➢ A variety of Non-human manufactured oligosaccharides tested in preterm infants.

➢ Short chain galacto-Oligos (scGOS);
Long chain fructo-Oligos (lcFOS);
Pectin-derived Oligos (pAOS)

Short Chain Fatty acids

Therapeutic Potential of Gut Microbiota and Its Metabolite Short-Chain Fatty Acids in Neonatal Necrotizing Enterocolitis

- Produced by “Good bacteria”.
- Bifidobacteria/Clostridia use HMO’s for growth and secrete SCFA.
- SCFA sustain mucosal barrier, regulate immunity and suppress inflammation.

Take home: Interesting!
Quick Takes

- Polyunsaturated fatty acids
  - n-3 long chain PUFA: 11 trials, N>1700 infants, No reduction in NEC rates.
- Enteral glutamine supplementation - No reduction in NEC
- Enteral arginine in small trials reduced NEC (moderate certainty)
- Oral administration of IgA and IgG – did not reduce NEC.
- **Future:** Direct Toll Like Receptor Antagonism – used novel peptides/nanoparticles ??
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Microbiome in NEC

Summary

Prenatal influences – Long term consequences

NEC associated microbiota patterns include:
- Gammaproteobacterial excess (Gram-ve)
- Decreased diversity & Bifidobacteria
- Effect of formula feeding/delivery mode

Evidence for dysbiosis and late-onset sepsis

(Cuna/Sampath et al. AJP Gastro and Hepatol April 2021)
Breast Milk - Nutrition, Anti-pathogen Immunity, Symbiosis

Human Milk Oligosaccharides: Glycosylated non-digestible sugars that are used by ONLY good bacteria (Bifidobacteria)


# Preterm formula vs. Donor EBM for premies – Neurodevelopmental outcomes

<table>
<thead>
<tr>
<th>Centres</th>
<th>Cambridge, Ipswich, King’s Lynn 502</th>
</tr>
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<tbody>
<tr>
<td>No randomised</td>
<td></td>
</tr>
<tr>
<td>Neonatal diets assigned</td>
<td></td>
</tr>
<tr>
<td>randomly</td>
<td></td>
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<tr>
<td><strong>Trial A</strong>: Diets used as sole enteral feed (mother chose not to provide her EBM)</td>
<td>BBM vs PTF</td>
</tr>
<tr>
<td><strong>Trial B</strong>: Diets used as supplements to mother’s EBM</td>
<td>BBM (+EBM) vs PTF (+EBM)</td>
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## Developmental test

<table>
<thead>
<tr>
<th>Diet</th>
<th>Advantage for PTF (95% CI)</th>
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<tbody>
<tr>
<td>BBM</td>
<td></td>
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<tr>
<td>PTF</td>
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**Trials**

- **Trial A**
  - n = 62
  - MDI 94.8 (2.1)
  - PDI 93.0 (1.8)
- **Trial B**
  - n = 139
  - MDI 102.2 (1.7)
  - PDI 95.5 (1.3)
- **Trials A plus B**
  - n = 196
  - MDI 99.9 (1.3)
  - PDI 94.7 (1.1)

A randomised multicentre study of human milk versus formula and later development in preterm infants A Lucas, R Morley, T J Cole, S M Gore

*Archives of Disease in Childhood* 1994; 78: F141–F146

**Preterm formula vs. breast milk (donor) no adverse 18 month neurological outcomes**
Donor or Formula for supplementation of MOM and 24 month outcomes; O’Connor et al. 2016 JAMA Pediatrics

- Effect of Donor human milk vs. Formula for MOM shortfall. 18 month neurodevelopmental outcome was primary outcome.

- No differences in growth and head circumference at 24 months.

Take home: DHM does not confer improved 24 month outcomes, trend towards worse neurological outcomes with DHM (need further studies).

Courtesy of Nick Embleton, MD Neonatologist (Newcastle upon Tyne, UK)
No increase in any negative outcomes with earlier refeeding. NEC and post-NEC stricture improved with early re-feeding

➢ Early re-feeding (<5 days or < 7 days) after NEC onset not associated with worse medical NEC outcomes.

➢ Trend towards less strictures, early discharge with early feeds; No change in mortality. Bias: More severe NEC and later re-feeding.

➢ Early refeeding safe in infants who develop stage I/IIA NEC; possibly safe in stage IIB NEC if pneumatosis has resolved.
NEC ischemia perfusion and TANEC


   - No RCT. 11 case-control studies; NEC associated with PRBC transfusion <48hr. TANEC infants less mature, 500gm heavier, PDA, etc. More severe disease.

   - Canadian neonatal research network; 2003-08, All NEC (n=927), controls- 2700. PRBC <48 hrs higher in cases vs. controls (15% vs. 7.5%). TANEC cases were smaller and less mature, higher SNAP-II-scores.
   - Outcomes for TANEC vs. other NEC no different for mortality/CNS injury/ROP.
Feeding in high-risk premature infants - ADEPT trial

- Leaf et al., Pediatrics April 2012; N=404; UK; 52 centers.
  - Infants < 35 week with Absent or reversed diastolic flows, <10% centile for weight randomized.
  - Feeds early **Day 2** vs. Late **Day 6**; once started similar rate of increase.
  - MOM 77% at start on Day 2 vs. 89% at start on Day 6.
  - Full feeds reach 18 days vs. 21 days. (p=0.008).
  - No effect on NEC (18% vs. 15%; stage III NEC 3 vs 5%). Less cholestasis with early feeding.

Courtesy of Nick Embleton, MD (Newcastle upon Tyne)
TANEC - Transfusion? Anemia? Or Both?

- More PRBC TRx for maintaining high Hgb did not result in more NEC.
- Trend towards more NEC in restrictive PRBC transfusion group.


? Is there an interaction between PRBC transfusions and anemia in causing NEC

- Prospective multi-center, observational study of anemia (Hgb≤8.0g/dl), PRBC transfusions, and NEC stage II+ (Patel RM, JAMA 2016; 315 (9)).
- 600 VLBW infants, NEC=44 (7.4%), 319 infants transfused (1430 TRx).
Feeding during PDA medical treatment


- Retrospective chart review: (Group A: NPO, n=229); Group B<60ml/kg/d (n=142); Group C:>60 ml kg/d (n=44). Birth weight (A: 864±239; B: 847±202; C: 932±234 g). Postnatal age at Indomethacin (A: 5.3±2.9; B: 7.2±4.9; C: 15.4±6.6 days).

- Primary outcome NEC (A: 6.1%, B: 7.8% and C: 4.6%, respectively)


- Infants (N = 177, 26.3 ± 1.9 wk) were randomized at 6.5 ± 3.9 days to receive "trophic" feeds ("feeding" group, n = 81: indomethacin 80%, ibuprofen 20%) or no feeds ("fasting [nil per os]" group, n = 96: indomethacin 75%, ibuprofen 25%).

- NEC/perforation 13% (NPO) vs. 10% (feed). Time to 120ml/kg/day 3 days earlier.