Early Nutrition of the Preterm Baby

Dr Kenny McCormick
Oxford
UK
Conflict of Interests

- Research Funding
- UK NIHR
- Oxford Biomedical Research Centre
- Charities, AMR, BHF
- Industry – Danone, Nestle, Baxters
- I hold no shares or financial benefits
- Views expressed are my own
Conclusions

Day 1 PN with adequate protein & lipid

Day 1 Enteral feeds advanced quickly

Money talks
IN UK 70,000 babies born
Before 37 weeks gestation

8,000 born before 31 weeks
Clinical Senates provide strategic, independent advice and leadership support to the commissioning and provision of healthcare designed to best meet the needs of patients.

Thames Valley
2.5m
One of wealthiest parts of EU

14 units hosted by 13 Trusts
## Table 16. Neonatal mortality rate by county, CP rate per 1000 neonatal survivors among children weighing under 1500g at birth, children born 1984 to 2001 (excluding CP of postneonatal origin)

<table>
<thead>
<tr>
<th>County</th>
<th>Live births</th>
<th>Neonatal deaths</th>
<th>Neonatal Survivors</th>
<th>Children with cerebral palsy</th>
<th>Neonatal mortality rate</th>
<th>Cerebral palsy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate/1000 live births</td>
<td>95% CI</td>
<td>Rate/1000 neonatal survivors</td>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berks</td>
<td>1 984</td>
<td>403</td>
<td>1 581</td>
<td>78</td>
<td>203</td>
<td>186-221</td>
</tr>
<tr>
<td>Bucks</td>
<td>1 423</td>
<td>300</td>
<td>1 123</td>
<td>57</td>
<td>211</td>
<td>190-233</td>
</tr>
<tr>
<td>Northants</td>
<td>1 559</td>
<td>338</td>
<td>1 221</td>
<td>64</td>
<td>217</td>
<td>197-238</td>
</tr>
<tr>
<td>Oxon</td>
<td>1 127</td>
<td>146</td>
<td>981</td>
<td>48</td>
<td>130</td>
<td>111-150</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6 093</strong></td>
<td><strong>1 187</strong></td>
<td><strong>4 906</strong></td>
<td><strong>247</strong></td>
<td><strong>195</strong></td>
<td><strong>185-205</strong></td>
</tr>
</tbody>
</table>
Public Accounts Committee; Caring for Vulnerable Babies: The reorganisation of neonatal services in England
• **Premature** – delivery before 37 weeks completed gestation

• **Small for Gestational Age** – birth weight < 10% for gestational age & sex

• **Intrauterine Growth Retardation** – fetus, usually SGA and growth has been restricted

• **LBW** - < 2500g regardless of gestation
• **VLBW** - <1500g regardless of gestation
• **ELBW** - <1000g regardless of gestation
Very low birth weight admissions* in 2009-2016

* VLBW = Very Low Birth Weight
** ELBW = Extremely Low Birth Weight

Graph showing the increase in admissions over the years from 2009 to 2016.
Survival to discharge for infants born 23–25 weeks and admitted to neonatal units in England;

## Neonatal Mortality in SGA Infants

<table>
<thead>
<tr>
<th>Weight</th>
<th>37 to 38 weeks</th>
<th>39 to 40 weeks</th>
<th>41 to 42 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA* 2750 to 3999 g</td>
<td>3.0</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>SGA† 1500 to 2500 g</td>
<td>55.7</td>
<td>56.5</td>
<td>59.7</td>
</tr>
<tr>
<td>SGA &lt;1500 g</td>
<td>268</td>
<td>285</td>
<td>252</td>
</tr>
</tbody>
</table>

*Appropriate for gestational age
† Small for gestational age

† Data from Williams, RL, Creasy, RK, Cunningham, GC, et al. Obstet Gynecol 1982; 59:624.
Why is poor early growth a problem?

Widdowson & McCance 1963

Fig. 1.2. The effect of suckling rats in small and large groups on subsequent growth in weight. Arrow shows weaning and commencement of *ad libitum* feeding. ○, suckled in small groups; ●, suckled in large groups [8].
EPICure STUDY
Change in Weight and OFC Standard Deviation Scores

A population based study of outcomes of all infants born before 26 weeks in the UK and Ireland between March and December 1995

The percentage of preterm infants that are >2 SD below the mean weight for age increases from 14 to 55% from birth to discharge.

The cause of this growth restriction is multifactorial, but it has been estimated that about 50% of the variance in early postnatal growth can be attributed to nutrition.

Weight gain associated with neuro-developmental outcome

- NICHD 500-1000g
- Quartiles of weight gain

Ehrenkranz et al
Paediatrics 2006; 117(4) 1253-61
“the promotion of the best somatic growth possible in the period before the second or third birthday is the most we can do to ensure good brain growth”

First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants.

- Week 1 energy and protein intakes were each independently associated with Mental Development Index at 18 months.

- Every 10 kcal/kg per day were associated with a 4.6-point increase in MDI & each g/kg per day in protein intake with an 8.2-point increase in MDI

- Higher protein intake was associated with lower likelihood of length<10th percentile.

- Emphasis should be placed on providing more optimal protein and energy during this first week.

Necrotising Enterocolitis
Fear of NEC?

- Affects 7% of VLBW infants (Lemons et al, Pediatrics 2001)
- Has >20% mortality (in BPSU surveys 1981-2 & 1993-4)
- Has drastic effects on nutrition, cholestasis
- Effects extend well beyond the gut
- 90% of babies who develop NEC are receiving enteral feeds
- As more extreme preterm babies survive the incidence of NEC has increased
Does NEC occur more frequently in IUGR Babies?

- Case-control study of 74 cases of NEC in preterm infants: at 30-36 weeks GA, birth weight<10th c, significant factor: OR 6 (1.3-26)

- Observation study Oxford 1985-91: 69 cases of definite/proven NEC. At 30-36 weeks 71% <10th centile (49% overall)
Does NEC occur more often after fetal Absent or Reversed End Diastolic Flow?

• 14 reviews comparing NEC rates in babies born after AREDFV

• 9 studies showed excess of NEC in babies with AREDFV: Odds Ratio 2.13 (95%CI 1.49-3.03)

Parenteral Nutrition

➢ Essential in the smallest, sickest babies
➢ The target is growth, not correction of malnutrition
➢ Standard regimens feasible
➢ Often Partial (not Total) PN, bridging the gap to full milk feeds
➢ Documentation poor and variable
➢ Prescribing and dispensing processes variable
➢ Complications common
National Confidential Enquiry into Patient Outcome and Death (NCEPOD)

A Mixed Bag: An enquiry into the care of hospital patients receiving parenteral nutrition (2010)

Results for neonates
What did we know?

• Role
  • to bridge the gap of functional gut immaturity until enteral nutrition can be established
    *Pediatrics* 1985; 75: 976

• Goal
  • approximation to normal intra-uterine and postnatal growth
    *J Pediatr Gastroenterol Nutr* 2010 50:1

• Evidence
  • For ELBW start early with rapid progression to full nutritional value
    *Semin Perinatol* 2007 31:48

• Guidelines
  • ESPGHAN, ESPEN, ESPR
Demographics

- 264 neonates from 74 hospitals
- 155 (59%) were of 30 weeks gestational age or less
- 93% on neonatal units (NU) in L3 or L2
- 191 immaturity of gut function
- 24 necrotising enterocolitis
Figure 3.5 Number of days for which PN was received
Quality of PN care

- 23.5% (62/264) Good Practice
- 4.5% (12/264) Less than satisfactory
Prescribing

- Most common reasons for inadequate PN constituents:
  - Insufficient amino acid and / or lipid content
  - And / or too slow progression
- Inadequacy of PN not dependent on the type of PN formulation

Table 3.23 Advisors’ opinion on the adequacy of the first PN for the patients’ needs

<table>
<thead>
<tr>
<th>PN adequate</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>112</td>
<td>62.9</td>
</tr>
<tr>
<td>No</td>
<td>66</td>
<td>37.1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>178</strong></td>
<td></td>
</tr>
<tr>
<td>Unknown/insufficient data</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>264</strong></td>
<td></td>
</tr>
</tbody>
</table>
### TPN by day 3 of Life: April 2011- March 2012

<table>
<thead>
<tr>
<th>Hospital</th>
<th>CQUIN</th>
<th>Network Measure</th>
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<tbody>
<tr>
<td></td>
<td>Received TPN by Day 3 of life</td>
<td>Received TPN by Day 2 of life</td>
</tr>
<tr>
<td>Queen Alexandra Hospital, Portsmouth</td>
<td>94</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>82%</td>
<td>53%</td>
</tr>
<tr>
<td>Princess Anne Southampton</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>88%</td>
<td>81%</td>
</tr>
<tr>
<td>John Radcliffe, Oxford</td>
<td>78</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>72%</td>
<td>53%</td>
</tr>
<tr>
<td>Wexham Park, Slough</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>51%</td>
</tr>
<tr>
<td>Royal Berkshire, Reading</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>63%</td>
<td>50%</td>
</tr>
<tr>
<td>Stoke Mandeville</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td>34%</td>
</tr>
<tr>
<td>Milton Keynes General</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>71%</td>
<td>66%</td>
</tr>
<tr>
<td>Grand Total</td>
<td>444</td>
<td>337</td>
</tr>
<tr>
<td></td>
<td>71%</td>
<td>54%</td>
</tr>
</tbody>
</table>

**Criteria:**

- Gestation < 30 weeks OR Birthweight < 1501g
- Infant admitted to unit < Day 3 of life
- Infant discharged from unit > Day 3 of life
- Infant discharged during time period

**How to ensure change?**

Commissioners demand standards of nutritional care
Optimal nutrient requirements for preterm babies are not known

**Intrauterine** nutrient provision
- lipid - minimal
- glucose - moderate
- amino acid – high

**Postnatal** nutrient provision
- lipid - high
- glucose - high
- protein - low

But sub-optimal practice can be recognised!
Lack of focus: Don’t give what you intend
Lack of knowledge: Don’t know what to give
Complex sick infant: Don’t use what you give

Poor nutritional outcome

Poor brain outcomes
Standardized, Concentrated with Added Macronutrients Parenteral (SCAMP) Nutrition Trial

All babies (<29/40) started on control PN by 6h
Randomised at 150ml/kg/d (d 3-8)
Care givers blinded
Pharmacists unblinded
N=150
SCAMP 11% more total protein
SCAMP 7% more total energy

No difference in preterm complication rate
SCAMP had higher OFC at 28 days and 36 weeks corrected

Morgan et al Paediatrics 2014;133: e120-8
Nutritional Evaluation and Optimisation in Neonates (NEON)

Preterm more likely to develop precursor conditions of metabolic syndrome
Low protein-energy ratio diet in preterms increases adipose tissue
Composition of weight gain may be more important than weight gain

Milk introduced in first 24 hours

161 infants < 31/40. 2x2 trial

Randomised to either immediate full RDI protein (3.2g/kg/d = 3.6g/kg/d AA) on day 1 life or incremental (1.5g/kg/d day 1 to 2.7g/kg/d by day 3)

AND

Lipid (2g/kg/d on day 1, 3g/kg/d from day 2) as either 20% intralipid or 20% SMOF

Primary outcome: body composition.
➢ Non-adipose or lean mass by whole-body MRI.
➢ The efficacy of lipid composition was assessed by MRS to measure intra-hepatocellular lipid content.

Uthaya et al, Efficacy & Mechanism Evaluation 2016;3(2)
Nutritional Evaluation and Optimisation in Neonates (NEON)

No difference in primary outcome;
   No differences in lean mass amounts
   No difference in intra hepatocellular lipid

No difference in secondary outcomes including biochemistry
Except
   ➢ Immediate group had higher urea > 7 mmol/l [75% vs. 49%] >10 mmol/l [49% vs. 18%] (p < 0.01)].
   ➢ Head circumference at term was smaller in the immediate group (mean difference −0.8 cm, 95% CI −1.5 to −0.1 cm; p = 0.02).

❖ results do not support the calls for more aggressive nutrition in the extremely preterm infant nor the routine use of SMOF lipid as reflected in international consensus statements (higher amounts of amino acids) or as is increasingly seen in current practice”

❖ use of standard PN regimen is feasible

❖ standardised regimens that have been tested in the context of a randomised controlled trial should be adopted in routine clinical practice to reduce the clinical risk to infants from variation in practice.
The real message

If on the first day of life you give:

➢ No parenteral nutrition

or

➢ less than 1.5g/kg/d of protein

or

➢ less than 2g/kg/d of lipid

You are already giving less nutrition than the bottom of the range currently under investigation by experts in the field.
Swedish babies < 27 weeks gestation
Effects of energy intake on Retinopathy of Prematurity

Average increase of 10kcal/kg/day led to 24% reduction in ROP after controlling for known confounders

Adjusted for birth weight, mechanical ventilation and blood transfusions.

Stoltz Sjöström et al. ADC 2016 Mar; 101(2): F108–F11
Additional risks of PN

Parenteral nutrition, (whether administered centrally or peripherally) (IRR 13.8, 95% CI 8.5 to 22.3, p<0.001)

and

gestational age < 26 weeks (IRR 2.4, 95% CI 1.7 to 3.5, p<0.001)

are the highest significant independent risk factors for newborn late onset blood stream infection

(Modì et al 2006)
Take home messages

➢ Start PN on 1\textsuperscript{st} day of life in babies <30 weeks gestation or <1000g

➢ Start protein at 1.5 – 2.0 g/kg/d and increase to 2.7 – 3.5g/kd/d by day 3

➢ Start lipid at 2g/kg/d on 1\textsuperscript{st} day of life and increase to 3g/kg/d by day 2

➢ No evidence that SMOF better than intralipid?

➢ Standardised bags are suitable for almost all babies and may be safer

➢ Standardised bags take less time to manufacture and should be cheaper

Milk feeds on day 1...
WHO recommendations for stable VLBW infants with birth weight between 1.0 and 1.5 kg.
Relevant for resource-limited settings*

- Infants who cannot be fed mother's own milk or donor human milk should be given preterm infant formula if they fail to gain weight despite adequate feeding with standard infant formula

- Infants who are fed mother’s own milk or donor human milk should not routinely be given bovine milk-based human milk fortifier*

- Infants who fail to gain weight despite adequate breast milk feeding should be given human-milk fortifiers, preferably those that are human milk based

- Infants should be given 10 ml/kg per day of enteral feeds, preferably expressed breast milk, starting from the first day of life, with the remaining fluid requirement met by intravenous fluids*

- Feed volumes can be increased by up to 30 ml/kg per day with careful monitoring for feed intolerance

WHO e-Library of Evidence for Nutrition Actions (eLENA) accessed 24/2/18
Follow up of cohort of babies who received either standard or preterm formula

Adolescents (16y) who received preterm formula on average 8 point higher verbal IQ

Brain volumes equal

Significant increase in caudate nucleus size

Mirrors previous relationship between caudate size and IQ in ex-prem 7 year olds*

Isaacs et al Pediatric Research 63, 308–314 2008

### Trophic feedings for parenterally fed infants

**Tyson & Kennedy 2005**

#### Trophic vs no feedings: 10 studies — 617 patients

- Started day 1 – day 8,
- Trophic feeds of 12-24mls/kg/day for 5-10 days
- Controls no feeding for 6-18 days
- Reduction in days to full feeds (WMD - 2.6 days) and length of hospitalisation (WMD - 11.4 days)
- No significant difference in NEC

#### Trophic vs progressive feeding: 1 study, 144 patients

- Trophic took longer to reach full feeds (WMD +13.4 days) and longer hospitalisation (WMD +11.0 days). ‘…trophic feedings associated with a marginally significant reduction in NEC (relative risk =0.14 [0.02, 1.07]; risk difference = -0.09 [-0.16, -0.01].’
- Trial terminated early because of increased NEC, 7/70 progressive vs 1/70 trophic, p<0.03

*Berseth 2003*
Milk stimulates local growth factor production in the gut;

glucagon-like peptide 2 (GLP-2),
gastrin,
cholecystokinin,
peptide YY,
neurotensin
Lack or absence of enteral nutrients

- Diminished intestinal size and weight
- Atrophy of intestinal mucosa
- Delayed maturation of intestinal enzymes
- Increased intestinal permeability and bacterial translocation
- Delayed maturation of intestinal motor activity and intestinal motility
- Lack of hormonal response
Trophic – from Ancient Greek *trophikós*, “pertaining to food or nourishment”.

**Adjective**
1. Of or pertaining to nutrition.
2. Of or pertaining to growth.
Minimal enteral nutrient requirements for intestinal growth in neonatal piglets: how much is enough?

- Jejunal wet weight, protein mass, and villus height were significantly greater at enteral intakes > 40%

- Stimulation of ileal protein mass required a higher enteral intake (60%)

- In both segments, abrupt increases in DNA mass, crypt depth, ornithine decarboxylase activity, and crypt cells in S-phase occurred between enteral intakes of 40% and 60%

- Concentrations of glucagon-like peptide-2 and peptide YY, but not gastrin, increased significantly between enteral intakes of 40% and 60% and closely paralleled indexes of cell proliferation

- Less than 40% as enteral intake does not have significant intestinal trophic effects

Burrin et al. Am J Clin Nutr June 2000 vol. 71 no. 6 1603-1610
Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies

• Standardised feeding regimens may provide the single most important global tool to prevent/minimise NEC in preterm neonates.

• Randomised controlled trials are needed

NPEU Oxford

Patole & de Klerk Archives of Disease in Childhood Fetal and Neonatal Edition 2005;90:F147-F151
When should we start milk feeds in a high risk population?
Day 2 versus day 6 of life
When should enteral feeds be started in small for gestational age preterm babies who had abnormal umbilical artery Doppler studies in utero?

• ‘... we have embarrassingly limited data on which to base decisions about when to start enteral feedings’

• ‘... it is unclear whether high-risk infants should receive early or delayed feedings’

• Tyson JE, Kennedy KA. 2005
Trial Population & Study Design

• Premature babies (≤34 weeks + 6 days) with abnormal antenatal Doppler studies

• Small for gestational age (birth weight <10th centile for gestational age based on Child Growth Foundation Charts)

• Randomised to start feeds early (24 - 48h) or late (120 – 144h) after birth

• Enteral prescription guideline – same rate of feed increment

• Primary outcomes
  • Days to establish full Enteral Feeding (3 days at 150ml/kg/d)
  • Incidence of Necrotising Enterocolitis
Study Power and Recruitment Plan

• Plan to recruit 400 babies based on study power calculations for primary outcomes:
  
  • to detect a 3 day difference in time to full enteral feeds (90% power, 0.05 significance)

  • to detect a reduction in NEC incidence from 15% to 7.5% (60% power, 0.05 significance)
<table>
<thead>
<tr>
<th></th>
<th>Early feeding</th>
<th></th>
<th>Late feeding</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>202</td>
<td></td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Gestation (w) Mean [SD]</td>
<td>31.2 [2.4]</td>
<td></td>
<td>31.1 [2.3]</td>
<td></td>
</tr>
<tr>
<td>Birthweight (g) Mean [SD]</td>
<td>1042 [302]</td>
<td></td>
<td>1018 [308]</td>
<td></td>
</tr>
<tr>
<td>Caesarean (%)</td>
<td>97</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Ventilated at randomisation (%)</td>
<td>13</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>CPAP at randomisation (%)</td>
<td>34</td>
<td></td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>UAC in situ at randomisation (%)</td>
<td>13</td>
<td></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>UVC in situ at randomisation (%)</td>
<td>27</td>
<td></td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>51</td>
<td></td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>
Day on which feeds commenced
compliance with intervention

Received Breast Milk at first feed

- Early feeding: 86%
- Late feeding: 90%
In 127 infants who weighed <1250 g in a Prospective Cohort Study, enteral feeding that contained at least 50% maternal human milk reached 150ml/kg/d 5 days sooner than babies with human milk intake <50%

### ADEPT Trial feeding regimes

<table>
<thead>
<tr>
<th>Feed regimen</th>
<th>‘early’</th>
<th>‘late’</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24 hours: day 1</td>
<td>Nil by mouth</td>
<td>Nil by mouth</td>
</tr>
<tr>
<td>24-48 hours: day 2</td>
<td>Start milk feeds</td>
<td>Nil by mouth</td>
</tr>
<tr>
<td>48-119 hours: day 3-5</td>
<td>Progress with feeding</td>
<td>Nil by mouth</td>
</tr>
<tr>
<td>120-143 hours: day 6</td>
<td>Progress with feeding</td>
<td>Start milk feeds</td>
</tr>
<tr>
<td>144 hours onwards – day 7+</td>
<td>Progress with feeding</td>
<td>Progress with feeding</td>
</tr>
<tr>
<td>Day of feeding</td>
<td>Volume of milk according to birth weight (ml/kg/HOUR)</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;600g</td>
<td>600-749g</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>8</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>9</td>
<td>3.5</td>
<td>4.0</td>
</tr>
<tr>
<td>10</td>
<td>4.0</td>
<td>4.5 - 5.0</td>
</tr>
<tr>
<td>11</td>
<td>4.5 - 5.0</td>
<td>5.5 - 6.0</td>
</tr>
<tr>
<td>12</td>
<td>5.5 - 6.0</td>
<td>6.25</td>
</tr>
<tr>
<td>13</td>
<td>6.25</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
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</tr>
</tbody>
</table>
Conclusions

• Early feeding group
  • Established feeds earlier (mean 3 days)
  • Had no increase in NEC or sepsis
  • Had less growth failure

• Late feeding group
  • Established feeds later
  • Received more days of parenteral nutrition
  • Received more days of high dependency care
  • Had increased incidence of cholestatic jaundice
  • Had no increase in NEC or sepsis
Time to full feeds by birthweight group

- **Statistical test of interaction p = 0.37**

**Graph Description:**
- X-axis: Time to full enteral feeding [days]
- Y-axis: Percentage with feeding established

**Legend:**
- Early feeding birthweight <750g (n=32)
- Late feeding birthweight <750g (n=34)
- Early feeding birthweight 750-999g (n=62)
- Late feeding birthweight 750-999g (n=61)
- Early feeding birthweight 1000-1249g (n=41)
- Late feeding birthweight 1000-1249g (n=45)
- Early feeding birthweight >=1250g (n=54)
- Late feeding birthweight >=1250g (n=42)
Feeding infants <29 weeks gestation with abnormal antenatal doppler

- Infants <29/40 were 22% of study population but contributed 50% cases of NEC
- No differences between early and late starters
- NEC was halved if received at least 50% as breast milk before full feeds achieved
- Median age to reach 150ml/kg/d was 28 days
- 90% had at least one episode of feed intolerance
- Stage 2 or 3 NEC 18% (v 6% for >29/40)
Fast v Slow (30 ml/kg/day) v (18 ml/kg/day)
daily increase in milk feed volumes
on
survival without moderate or severe disability at 24 months PMA in
very preterm (<32 weeks) or VLBW infants
A balancing act?
Baseline Data Collection: daily recording of type and quantity of milk given, episodes of infection, antibiotics administered, major morbidity and mortality

Outcomes Until Hospital Discharge
- Incidence of microbiologically-confirmed or clinically suspected late-onset invasive infection from trial entry until hospital discharge
- Incidence of necrotising enterocolitis (Bell stage 2 or 3)
- Time taken to reach full milk feeds (tolerating 150 ml/kg/day for 3 consecutive days)
- Duration of parenteral feeding before discharge
- Length of time in intensive care
- Length of hospital stay

Follow-up at 2 Years (Via Parent Report Questionnaire)

Primary outcome - survival without severe or moderate disability
Data collection to report outcomes regarding physical and mental development
Power Calculation 1

• PO = proportion of infants surviving without moderate or severe disability at 24 months of age corrected for prematurity

• estimated 80% survival to two years

• estimated proportion surviving without moderate or severe disability in the slow group will be 71%
Power Calculation 2

• 2,500 infants (1,250 per arm) to give 90% power to detect an **absolute difference** in proportions (two-sided 5% significance) of:

  • **5.7%** difference in survival without moderate/severe disability
    • e.g. 71.0% in slow group -> 76.7% in fast

  • **5.4%** difference in incidence of sepsis
    • e.g. 25.0% in slow group -> 19.6% in fast

  • **3.5%** difference in the incidence of NEC stage 2 or 3
    • e.g. 6.0% in slow group -> 9.5% in fast
Final sample size; 2800

• Inflation factor of 1.12 applied to sample size

• Allow for multiples receiving the same allocation & correlation in outcome

• Estimate
  • 25% multiples
  • intraclass correlation coefficient of 0.9 for PO at two years

LAMBS study data, Johnson, ADF&N 2015
Pragmatic Study

• Aimed to increase feeds over 5 or 9 days according to tolerance
• Unit based protocols for other aspects of feeding & care
• Updated final analysis since previous presentations

• Protocol and much more at https://www.npeu.ox.ac.uk/sift
Infant information collected at trial entry
(Minimisation factors highlighted)

<table>
<thead>
<tr>
<th></th>
<th>Fast (30 ml/kg/day) (n=1394)</th>
<th>Slow (18 ml/kg/day) (n=1399)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of centres, n (%):</strong></td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>739/1394 (53.0)</td>
<td>726/1398 (51.9)</td>
</tr>
<tr>
<td><strong>Infant age (days): Median {IQR}</strong></td>
<td>4 {3, 6}</td>
<td>4 {3, 6}</td>
</tr>
<tr>
<td><strong>Birth weight less than 10th centile for gestational age, n (%):</strong></td>
<td>295/1394 (21.2)</td>
<td>291/1398 (20.8)</td>
</tr>
<tr>
<td><strong>Gestation at delivery (completed weeks)</strong></td>
<td>In Figure</td>
<td>In Figure</td>
</tr>
<tr>
<td><strong>Weight at trial entry (grams):</strong></td>
<td>In Figure</td>
<td>In Figure</td>
</tr>
</tbody>
</table>
Gestational Ages

The chart illustrates the distribution of gestational ages along with data on fluid consumption. The categories range from 23+0 to 23+6, 24+0 to 24+6, 25+0 to 25+6, and so on, with bars indicating fluid intake for two different rates: Fast (30 ml/kg/day) and Slow (18 ml/kg/day). The graph visually represents the correlation between gestational age and fluid intake rates.
Weights at Trial Entry

- **<500g**
- **500 to 749g**
- **750 to 999g**
- **1000 to 1249g**
- **1250 to 1499g**
- **≥1,500g**

**Fast (30 ml/kg/day)**

**Slow (18 ml/kg/day)**
Outcomes at hospital discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fast (30ml/kg/day) (n=1394)</th>
<th>Slow (18ml/kg/day) (n=1399)</th>
<th>Effect measure(^a) (95% CI)</th>
<th>Adjusted(^b) effect measure (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiologically-confirmed or clinically suspected late-onset invasive infection from trial entry until hospital discharge, n (%) and risk ratio:</td>
<td>414/1389 (29.8 %)</td>
<td>434/1396 (31.1 %)</td>
<td>0.96 (0.85 to 1.08)</td>
<td>0.96 (0.86 to 1.07)</td>
</tr>
<tr>
<td>NEC (Bell stage 2 or 3) from trial entry until hospital discharge, n (%) and risk ratio:</td>
<td>70/1394 (5.0 %)</td>
<td>78/1399 (5.6 %)</td>
<td>0.90 (0.66 to 1.24)</td>
<td>0.88 (0.68 to 1.16)</td>
</tr>
</tbody>
</table>

\(^a\) 95% confidence intervals for late-onset infection and NEC. 99% confidence intervals for all other outcomes.

\(^b\) Adjusted for minimisation factors; hospital, single or multiple birth, gestational age at birth, and birth weight < 10th centile for gestational age.
### Short-term outcomes at hospital discharge

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>Fast (30ml/kg/day) (n=1394)</th>
<th>Slow (18ml/kg/day) (n=1399)</th>
<th>Effect measure (99% CI)</th>
<th>Adjusted(^b) effect measure (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before discharge home, n (%) and risk ratio:</td>
<td>60/1392 (4.3%)</td>
<td>65/1393 (4.7%)</td>
<td>0.92 (0.59 to 1.45)</td>
<td>0.91 (0.55 to 1.53)</td>
</tr>
<tr>
<td>Time taken to reach full milk feeds from trial entry (tolerating 145ml/kg day for 3 consecutive days): Median time to event percentiles {25(^{th}), 75(^{th})} and hazard ratio (to FF)</td>
<td>7 {7, 10}</td>
<td>10 {9, 13}</td>
<td>1.69 (1.53 to 1.87)*</td>
<td>1.93 (1.73 to 2.15)</td>
</tr>
</tbody>
</table>

Unknown 53 67
Time to reach full milk feeds
Kaplan-Meier survival estimates

Days from trial entry

Slow increase (18 ml/kg/day)
Fast increase (30 ml/kg/day)
# Short-term outcomes at hospital discharge

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>Fast (30ml/kg/day) (n=1394)</th>
<th>Slow (18ml/kg/day) (n=1399)</th>
<th>Effect measure (99% CI)</th>
<th>Adjusted effect measure (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Standard Deviation Score (SDS) at hospital discharge: Mean [SD] and mean difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.5 [1.1]</td>
<td>-1.5 [1.1]</td>
<td>-0.04 (-0.15 to 0.08)</td>
<td>-0.02 (-0.11 to 0.08)</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head circumference Standard Deviation Score (SDS) at hospital discharge: Mean [SD] and mean difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.8 [1.5]</td>
<td>-0.7 [1.7]</td>
<td>-0.09 (-0.27 to 0.09)</td>
<td>-0.07 (-0.24 to 0.10)</td>
<td></td>
</tr>
<tr>
<td>228</td>
<td>228</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of parenteral feeding from trial entry to discharge home: Median [IQR] and median difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2.00 (-2.44 to -1.56)*</td>
<td>-2.15 (-2.72 to -1.58)*</td>
<td></td>
</tr>
<tr>
<td>9 (7, 14)</td>
<td>11 (9, 16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of time in intensive care from trial entry to discharge home: Median [IQR] and median difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1.00 (-2.62 to 0.62)</td>
<td>-0.43 (-1.49 to 0.63)</td>
<td></td>
</tr>
<tr>
<td>7 (4, 21)</td>
<td>8 (4, 21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of hospital stay from trial entry to discharge home: Median [IQR] and median difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1.00 (-5.16 to 3.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>54 [37, 81]</td>
<td>55 [38, 78]</td>
<td>0.05 (-1.89 to 2.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What about subgroups?
What about subgroups?

- None of the prespecified analyses are statistically significant!

Gestation
Birth weight
Type of milk
Conclusions from SIFT

• Faster fed babies (30ml/kg/day) achieved full feeds quicker, and received less PN.

• No evidence of harm from faster feeding, sepsis not increased and may be reduced, NEC reassuringly lower in fast group.

• Clinical decisions to make!

• NPEU Oxford
Next Steps

- Complete other analyses
  - Health Economics comparison
    - 10,000/yr, -2 days PN (£50/day) = £1 mill/year saving in UK
  - Follow-up & 2 year outcomes
    - Important primary outcome
    - PARCA-R questionnaire
    - Other data sources
    - Currently just over 80% response
- Cochrane analysis update
Acknowledgements; NPEU team and CIG

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• Christina Cole
• Vasha Bari
• Andy King
• David Murray
• Louise Linsell
• John Townend
• Omar Omar
• Ursula Bowler
• Ed Juszczak

• TSC & DMC

• Jane Abbott
• Janet Berrington
• Elaine Boyle
• John Dorling
• Nicholas Embleton
• Alison Leaf
• Samantha Johnson
• Kenny McCormick
• Bill McGuire
• Mehali Patel
• Tracy Roberts
• Ben Stenson
Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants (Review)

Oddie SJ, Young L, McGuire W

• Updated 30/08/17
9 other trials

• 949 infants

• North America
  • Rayyis 1999; Caple 2004

• India
  • Salhotra 2004; Krishnamurthy 2010; Mukhopadhyay 2014; Modi 2015

• Turkey
  • Karagol 2013

• South Africa
  • Raban 2014a; Raban 2014b.
Rates

• Rayyis 1999: 15 v 35 mL/kg;
• Caple 2004: 20 v 35 mL/kg;
• Salhotra 2004: 15 v 30 mL/kg;
• Krishnamurthy 2010: 20 v 30 mL/kg;
• Karagol 2013: 20 v 30 mL/kg;
• Mukhopadhyay 2014: 20 v 30 mL/kg;
• Raban 2014a: 24 v 36 mL/kg;
• Raban 2014b: 24 v 36 mL/kg;
• Modi 2015: 15 to 20 v 30 to 40 mL/kg.
Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants

MORTALITY

Figure 5. Forest plot of comparison: I Slow versus faster rates of feed advancement, outcome: 1.2 Mortality.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Slow rate Events</th>
<th>Fast rate Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FYI 1989</td>
<td>0</td>
<td>98</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Raban 2014A</td>
<td>13</td>
<td>51</td>
<td>19</td>
<td>15.4% 0.63 [0.35, 1.13]</td>
</tr>
<tr>
<td>SIFT 2015</td>
<td>66</td>
<td>1393</td>
<td>60</td>
<td>46.8% 1.08 [0.77, 1.53]</td>
</tr>
<tr>
<td>Raban 2014B</td>
<td>16</td>
<td>52</td>
<td>14</td>
<td>11.1% 1.19 [0.60, 2.01]</td>
</tr>
<tr>
<td>Karagol 2013</td>
<td>4</td>
<td>46</td>
<td>3</td>
<td>2.3% 1.33 [0.32, 5.63]</td>
</tr>
<tr>
<td>Modii 2015</td>
<td>28</td>
<td>65</td>
<td>20</td>
<td>15.5% 1.42 [0.90, 2.25]</td>
</tr>
<tr>
<td>Krishnamurthy 2010</td>
<td>6</td>
<td>50</td>
<td>4</td>
<td>3.1% 1.50 [0.45, 4.99]</td>
</tr>
<tr>
<td>Salhotra 2004</td>
<td>12</td>
<td>26</td>
<td>7</td>
<td>5.4% 1.78 [0.83, 3.81]</td>
</tr>
<tr>
<td>Jain 2016</td>
<td>3</td>
<td>15</td>
<td>0</td>
<td>0.4% 7.00 [0.39, 124.93]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1796</td>
<td>1780</td>
<td>100.0%</td>
<td>1.15 [0.93, 1.42]</td>
</tr>
<tr>
<td>Total events</td>
<td>147</td>
<td>127</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 8.03, df = 7 (P = 0.33); I² = 13%
Test for overall effect: Z = 1.25 (P = 0.21)

SIFT 1.09 (0.77 – 1.53)
note slow v fast in Cochrane
Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants

**INVASIVE INFECTION**

= confirmed sepsis (+ve culture & 5 days antibiotics)

Slow 267 / 1393 (19.2%)
Fast 247 / 1392 (17.7%)

RR 1.08 (0.92 – 1.26)
Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants

**NEC**

**Figure 3. Forest plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.1 Incidence of necrotising enterocolitis.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Slow rate Events</th>
<th>Total Events</th>
<th>Fast rate Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 All infants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rayis 1999</td>
<td>13</td>
<td>88</td>
<td>8</td>
<td>87</td>
<td>8.2%</td>
<td>1.44 [0.63, 3.32]</td>
<td>1999</td>
</tr>
<tr>
<td>Caple 2004</td>
<td>2</td>
<td>64</td>
<td>4</td>
<td>74</td>
<td>4.1%</td>
<td>0.44 [0.08, 2.34]</td>
<td>2004</td>
</tr>
<tr>
<td>Salhotra 2004</td>
<td>0</td>
<td>26</td>
<td>2</td>
<td>27</td>
<td>2.4%</td>
<td>0.21 [0.01, 4.12]</td>
<td>2004</td>
</tr>
<tr>
<td>Krishnamurthy 2010</td>
<td>1</td>
<td>50</td>
<td>2</td>
<td>50</td>
<td>1.9%</td>
<td>0.50 [0.05, 5.34]</td>
<td>2010</td>
</tr>
<tr>
<td>Karagol 2013</td>
<td>5</td>
<td>46</td>
<td>4</td>
<td>46</td>
<td>3.8%</td>
<td>1.25 [0.36, 4.36]</td>
<td>2012</td>
</tr>
<tr>
<td>Raban 2014b</td>
<td>9</td>
<td>52</td>
<td>2</td>
<td>50</td>
<td>2.0%</td>
<td>4.33 [0.98, 19.05]</td>
<td>2014</td>
</tr>
<tr>
<td>Raban 2014a</td>
<td>1</td>
<td>51</td>
<td>7</td>
<td>47</td>
<td>7.0%</td>
<td>0.13 [0.02, 1.03]</td>
<td>2014</td>
</tr>
<tr>
<td>Modi 2015</td>
<td>2</td>
<td>65</td>
<td>1</td>
<td>66</td>
<td>1.0%</td>
<td>2.03 [0.19, 21.85]</td>
<td>2015</td>
</tr>
<tr>
<td>SIFT 2016</td>
<td>78</td>
<td>1399</td>
<td>70</td>
<td>1394</td>
<td>67.7%</td>
<td>1.11 [0.81, 1.52]</td>
<td>2016</td>
</tr>
<tr>
<td>Jain 2016</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>15</td>
<td>1.3%</td>
<td>0.50 [0.05, 1.04]</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1886</strong></td>
<td><strong>1856</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td><strong>1.07 [0.83, 1.39]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 112

Heterogeneity: Chi² = 11.34, df = 9 (P = 0.25); I² = 21%

Test for overall effect: Z = 0.54 (P = 0.59)

SIFT 1.11 (0.81 – 1.52)
Conclusions

Day 1 PN with adequate protein & lipid

Day 1 Enteral feeds advanced quickly

Money talks
Final Observations

• The greatest current challenge in neonatal nutrition is providing adequate nutrition to the most vulnerable babies in the first weeks of life

• Regimens that support brain growth should be preferred

• Mothers own breast milk confers biological advantages
In childhood - NEC kills more children than all childhood leukaemia and lymphoma combined
NEC from trial entry until hospital discharge by week of gestation

<table>
<thead>
<tr>
<th>Necrotising enterocolitis</th>
<th>Fast (30 ml/kg/day) (n=1394)</th>
<th>Slow (18 ml/kg/day) (n=1399)</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation at delivery (weeks):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24, n (%)</td>
<td>6/30 (20.0)</td>
<td>8/31 (25.8)</td>
<td>0.78 (0.36 to 1.67)</td>
</tr>
<tr>
<td>24&lt;sup&gt;+&lt;/sup&gt; to 24&lt;sup&gt;+&lt;/sup&gt;6, n (%)</td>
<td>11/72 (15.3)</td>
<td>10/69 (14.5)</td>
<td>1.03 (0.45 to 2.32)</td>
</tr>
<tr>
<td>25&lt;sup&gt;+&lt;/sup&gt; to 25&lt;sup&gt;+&lt;/sup&gt;6, n (%)</td>
<td>18/103 (17.5)</td>
<td>9/101 (8.9)</td>
<td>1.75 (0.68 to 4.53)</td>
</tr>
<tr>
<td>26&lt;sup&gt;+&lt;/sup&gt; to 27&lt;sup&gt;+&lt;/sup&gt;6, n (%)</td>
<td>21/291 (7.2)</td>
<td>26/297 (8.8)</td>
<td>0.84 (0.55 to 1.29)</td>
</tr>
<tr>
<td>28&lt;sup&gt;+&lt;/sup&gt; to 29&lt;sup&gt;+&lt;/sup&gt;6, n (%)</td>
<td>12/377 (3.2)</td>
<td>17/383 (4.4)</td>
<td>0.72 (0.29 to 1.81)</td>
</tr>
<tr>
<td>30&lt;sup&gt;+&lt;/sup&gt; to 31&lt;sup&gt;+&lt;/sup&gt;6, n (%)</td>
<td>2/432 (0.5)</td>
<td>7/432 (1.6)</td>
<td>0.25 (0.05 to 1.22)</td>
</tr>
<tr>
<td>≥32&lt;sup&gt;+&lt;/sup&gt;, n (%)</td>
<td>0/89 (0.0)</td>
<td>1/86 (1.2)</td>
<td>-</td>
</tr>
</tbody>
</table>

Test for interaction p-value from adjusted model = 0.63

<sup>a</sup>The ≥32<sup>+</sup> group was combined with 30<sup>+</sup> to 31<sup>+</sup>6 for the statistical analysis.
NEC from trial entry until hospital discharge by birthweight centile

<table>
<thead>
<tr>
<th>Necrotising enterocolitis</th>
<th>Fast (30 ml/kg/day) (n=1394)</th>
<th>Slow (18 ml/kg/day) (n=1399)</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight Category:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10th centile for gestational age, n (%)</td>
<td>14/295 (4.7)</td>
<td>20/291 (6.9)</td>
<td>0.65 (0.35 to 1.21)</td>
</tr>
<tr>
<td>≥ 10th centile for gestational age, n (%)</td>
<td>56/1099 (5.1)</td>
<td>58/1107 (5.3)</td>
<td>0.97 (0.72 to 1.30)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Test for interaction p-value from adjusted model = 0.25
NEC from trial entry until hospital discharge by type of milk

<table>
<thead>
<tr>
<th>Necrotising enterocolitis</th>
<th>Fast (30 ml/kg/day) (n=1394)</th>
<th>Slow (18 ml/kg/day) (n=1399)</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Milk&lt;sup&gt;a&lt;/sup&gt;:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Milk Only, n (%)</td>
<td>28/381 (7.1)</td>
<td>30/391 (7.7)</td>
<td>1.04 (0.66 to 1.66)</td>
</tr>
<tr>
<td>Formula Only, n (%)</td>
<td>0/46 (0.0)</td>
<td>1/47 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Mixed, n (%)</td>
<td>42/964 (4.4)</td>
<td>46/959 (4.8)</td>
<td>0.83 (0.55 to 1.25)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Test for interaction p-value from adjusted model = 0.53

<sup>a</sup> The breast milk only group = EBM, DBM or EBM +/- Fortifier

<sup>b</sup> The formula only group was combined with the mixed group for the statistical analysis.
# NEC from trial entry by AREDF

<table>
<thead>
<tr>
<th>Necrotising enterocolitis</th>
<th>Fast (30 ml/kg/day) (n=1394)</th>
<th>Slow (18 ml/kg/day) (n=1399)</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDF identified:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, n (%)</td>
<td>62/1163 (5.3)</td>
<td>62/1154 (5.4)</td>
<td>1.00 (0.73 to 1.35)</td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>8/209 (3.8)</td>
<td>16/226 (7.1)</td>
<td>0.49 (0.23 to 1.06)</td>
</tr>
<tr>
<td>Unknown</td>
<td>22</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Test for interaction p-value from adjusted model = 0.09

NB: NOT A PRESPECIFIED ANALYSIS
Late-onset invasive infection from trial entry until hospital discharge by week of gestation

<table>
<thead>
<tr>
<th>Gestation at delivery (weeks):</th>
<th>Fast (30 ml/kg/day) (n=1394)</th>
<th>Slow (18 ml/kg/day) (n=1399)</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24, n (%)</td>
<td>21/30 (70.0)</td>
<td>24/31 (80.6)</td>
<td>0.94 (0.73 to 1.20)</td>
</tr>
<tr>
<td>24^0 to 24^6, n (%)</td>
<td>51/71 (71.8)</td>
<td>40/69 (58.0)</td>
<td>1.17 (0.92 to 1.49)</td>
</tr>
<tr>
<td>25^0 to 25^6, n (%)</td>
<td>68/101 (67.3)</td>
<td>63/100 (63.6)</td>
<td>1.04 (0.84 to 1.30)</td>
</tr>
<tr>
<td>26^0 to 27^6, n (%)</td>
<td>135/290 (46.6)</td>
<td>138/297 (47.5)</td>
<td>1.00 (0.87 to 1.16)</td>
</tr>
<tr>
<td>28^0 to 29^6, n (%)</td>
<td>91/376 (24.2)</td>
<td>95/382 (25.5)</td>
<td>0.99 (0.78 to 1.26)</td>
</tr>
<tr>
<td>30^0 to 31^6, n (%)</td>
<td>46/432 (10.6)</td>
<td>66/432 (15.3)</td>
<td>0.71 (0.47 to 1.07)</td>
</tr>
<tr>
<td>≥32^0, n (%)</td>
<td>2/89 (2.2)</td>
<td>8/86 (10.5)</td>
<td>0.23 (0.05 to 1.13)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Test for interaction p-value from adjusted model = 0.07
Late-onset infection from trial entry until hospital discharge by birthweight centile

<table>
<thead>
<tr>
<th>Late-onset invasive infection</th>
<th>Fast (30 ml/kg/day) (n=1394)</th>
<th>Slow (18 ml/kg/day) (n=1399)</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight Category:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10th centile for gestational age, n (%)</td>
<td>91/293 (31.1)</td>
<td>87/290 (30.8)</td>
<td>1.02 (0.84 to 1.22)</td>
</tr>
<tr>
<td>≥ 10th centile for gestational age, n (%)</td>
<td>323/1096 (29.5)</td>
<td>347/1106 (31.9)</td>
<td>0.94 (0.83 to 1.07)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Test for interaction p-value from adjusted model = 0.51
Late-onset infection from trial entry until hospital discharge by type of milk

<table>
<thead>
<tr>
<th>Late-onset invasive infection</th>
<th>Fast (30 ml/kg/day) (n=1394)</th>
<th>Slow (18 ml/kg/day) (n=1399)</th>
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</thead>
<tbody>
<tr>
<td><strong>Type of Milk</strong>:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Milk Only, n (%)</td>
<td>112/380 (29.8)</td>
<td>118/390 (30.3)</td>
<td>0.98 (0.79 to 1.22)</td>
</tr>
<tr>
<td>Formula Only, n (%)</td>
<td>11/46 (23.9)</td>
<td>7/47 (14.9)</td>
<td>1.53 (0.62 to 3.78)</td>
</tr>
<tr>
<td>Mixed, n (%)</td>
<td>289/961 (30.0)</td>
<td>308/958 (32.2)</td>
<td>0.93 (0.83 to 1.04)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Test for interaction p-value from adjusted model = 0.56

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a The breast milk only group = EBM, DBM or EBM +/- Fortifier
b The formula only group was combined with the mixed group for the statistical analysis.
Late-onset infection from trial entry until hospital discharge by AREDF

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Test for interaction p-value from adjusted model = 0.09

NB: NOT A PRESPECIFIED ANALYSIS