Is NEC requiring surgery precipitated by a change in feeds? Observations from 50 consecutive cases.

David Burge
SIGNEC September 2015
Clinical series
Specific cases
Other scenarios
Published experience
Breast milk and neonatal necrotising enterocolitis

A. Lucas  T. J. Cole

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Feed</th>
<th>Confirmed NEC % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucas 1990</td>
<td>RCT</td>
<td>Formula Mixed BM only</td>
<td>7.2% (236) 2.5% (437) 1.2% (253)</td>
</tr>
</tbody>
</table>

- breast feeding is protective against NEC
- effect may be dose-dependent
- Formula ➔ substrates for bacteria ➔ invade mucosa
Question

Is breast milk protective
or
are other feeds causative?
In babies with surgically proven NEC to examine:

- The feed type at time of NEC
- The temporal relationship between a change in feed type and development of NEC
Methods (1)

- Retrospective cohort study
- Identification of patients
  - Southampton Neonatal Surgical database
- Review of feed history
  - Badgernet data (100%)
  - Notes review
    - local (70%)
    - Southampton (100%)
Methods (2)

- **Included**
  - All preterm infants with acute NEC confirmed at surgery or post mortem April 2007 – Sept 2015

- **Excluded**
  - (Isolated perforation)
  - Term infants
  - Cardiac patients
  - Previous intestinal surgery
Results

Total surgical NEC • 66
Exclusions • 11
Number studied • 55
Gestation (wk) • 27 (23-33)
BW (g) • 877 (458-1995)
Age at NEC (d) • 30 (4-61)
Acute Mortality • 22 (40%)
### Abbreviations used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>BM</td>
<td>Breast milk</td>
</tr>
<tr>
<td>PTF</td>
<td>Preterm formula</td>
</tr>
<tr>
<td>BMF</td>
<td>Breast milk fortifier</td>
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<tr>
<td>EHF</td>
<td>Extensively hydrolysed formula (Pregestamil, Peptijunior, hydrolysed Nutriprem)</td>
</tr>
<tr>
<td>AAF</td>
<td>Amino-acid formula (Neocate)</td>
</tr>
</tbody>
</table>
Feeds at time of NEC

- Breast milk • 11%
- Formula • 31%
- Mixed feeds • 58%
  - BM + Formula • 31%
  - BM + BMF • 16%
  - BM + Formula + BMF • 11%
Propositions (1)

- 27% of NEC occurred in fully BF infants (6 BM only, 9 BM + BMF)
- Previous studies show ~ 10% NEC occurs in BF infants

This suggests that full BM feeds do not protect against NEC and that products in BMF may be causative
Time from first exposure of CMP to diagnosis of NEC (n=49)

- The median time from first exposure to CMP to NEC was 9 days (range 1-41).
- In 25 (51%) infants NEC occurred within a week of first exposure to CMP.
• 50% of infants with surgical NEC do so within 7 days of first exposure to non-human milk products, often after several weeks of stability.

This suggests a causative role for feeds other than BM
Why should non-human milk products increase the risk of NEC?
## Abbreviations used

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<tr>
<td>CMP</td>
<td>Cow’s milk protein</td>
</tr>
<tr>
<td>CMPI</td>
<td>CMP intolerance</td>
</tr>
<tr>
<td>CMPA</td>
<td>CMP allergy</td>
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<tr>
<td>BM-CMPF</td>
<td>BM – mother on CMP-free diet</td>
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</tbody>
</table>
Terminology

CMPA
IgE mediated

Asthma, eczema, atopy, chronic – 2-5% of infants

CMPA
IgE or Non-IgE

Non-IgE mediated

Intestinal, non-atopic, short term – 10-15% of infants
Non-IgE CMPA

Clinical features

• Numerous GI dysfunction symptoms

• Food protein induced enterocolitis syndrome (FPIES),
  – repetitive vomiting, hypotonia, pallor, diarrhoea.

• Cows milk-induced enteropathy syndrome
  – diarrhoea,
  – failure to thrive
  – vomiting
  – blood streaked stools.

• Cows milk-induced proctocolitis
  – rectal bleeding (usually flecks of blood) and occasionally mild diarrhoea in an otherwise healthy breast fed infant..

Clues from other scenarios (1)

Gastroschisis
Gastroschisis

- Congenital abdominal wall defect
- Mostly term infants but similar to preterm
  - Inherent intestinal dysmotility
  - Disordered enteral feeding
  - Increased intestinal permeability
In 111 infants with gastroschisis there were 64 episodes of suspected CMPA in 50 infants (45%).

Feed at the time of the episode:
- BM (24), term formula (20), EHF (6).

Partial or complete resolution of symptoms occurred in all following feed change to avoid CMP.

Recurrent episodes occurred in 13/50 infants (26%), 10 of whom were receiving EHF, none in infants on AAF.
Is AAF better than EHF?

- 10% - 30% of infants will react to residual peptides in EHF and require AAF *
- In infants with significant non-IgE mediated CMPA an AAF would be a safer choice *
- Infants who develop CMPA on BM may be better suited to AAF (BM bovine beta-lactoglobulin ~ EHF) **.

NEC in gastroschisis

- Reported in ~ 10% of cases
- “atypical” compared to preterm NEC
  - Later presentation often after discharge home *
  - More benign clinical condition **
  - ? Due to CMPA


Intramural gas in gastroschisis
(pneumatosis intestinalis - PI)

- Seen in 6 babies at the time that they exhibited clinical features on CMPA
- one had 2 episodes
- The feed at the time was BM in 2 infants and EHF in 4.
Intramural gas (PI) in CMPA

- PI recognised in many different clinical scenarios
- Many articles and textbooks comment on PI being associated with CMPA


Cycle of vulnerability

- Dysmotility
  - CMPA
  - Sepsis
    - Increased permeability
    - Bacterial overgrowth
  - Stasis
    - Inherent gastroschisis factors
Clues from other scenarios (2)

CMPA in a preterm neonate mimicking NEC
Case history:

- 26 week BW 855g.
- Maternal CMPA but tried drinking milk to improve BM value. Each occasion she developed abdominal distension and loose stools as did her baby.
- At 11 wks ➔ preterm formula. 2 days later developed abdominal distension with bloody stools and vomiting altered blood.
- NEC diagnosed but very well, hungry baby with no abdominal signs other than distension
- Re-graded successfully onto Neocate with rapid correction of poor growth
Is there any evidence for CMPA in NEC?
“Fulminant NEC immediately following change to LBW formula”

9 preterm infants developed fulminant NEC within 24hrs of exposure to PTF
## Bovine v human BMF

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<thead>
<tr>
<th>Author</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Cristofalo, E 2013</td>
<td>RCT of formula v BM + hBMF*</td>
<td>More surgical NEC in formula group but not significant (4 v 0)</td>
</tr>
<tr>
<td>Sullivan S, 2010</td>
<td>This compared human v bovine BMF and rates of surgical NEC</td>
<td>Bovine BMF may increase the risk of NEC</td>
</tr>
<tr>
<td></td>
<td>BM + hBMF/bBMF/formula</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/138 1.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7/69 10%</td>
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</tr>
</tbody>
</table>

* hBMF = BMF made from human milk
** bBMF = BMF made from bovine milk
## Laboratory support for non-IgE CMPA in NEC

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<th>Conclusion</th>
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<td>Chuang, S (2004)</td>
<td>NEC infants have a strong cytokine response to $\beta$LG* in peripheral blood mononuclear cells (MC)</td>
<td>Significant CMP sensitisation in NEC</td>
</tr>
<tr>
<td>Abdelhamid, A (2012)</td>
<td>In recovery from NEC the strong cytokine response to $\beta$LG is increased with introduction of feeds and further at full feeds</td>
<td>Significant CMP sensitisation in NEC</td>
</tr>
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* $\beta$LG = beta-lactoglobulin
“The studies ...have been valuable in raising the profile of cow’s milk as a trigger of intestinal inflammation in preterm neonates. Similar enhanced lymphocyte response to cow’s milk has been identified in infants with FPIES (11). ... It is possible that what begins as a relatively low-grade pathology can accelerate catastrophically due to unchecked immune regulation.”
### Mapping the New World of Necrotizing Enterocolitis


<table>
<thead>
<tr>
<th>NEC associated with delayed feeding</th>
<th>Transfusion associated NEC</th>
<th>Lymphocytosis associated NEC</th>
<th>Cows milk associated NEC</th>
<th>Term NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>perinatal antibiotics triggers poorly characterized delayed feeding</td>
<td>passive immunity to blood &amp; IEC antigens via transfusions</td>
<td>virus infection activation of TLRs &amp; apoptosis</td>
<td>sensitivity to cows milk protein in diet</td>
<td>hypoxia ischemia</td>
</tr>
<tr>
<td>skewed flora</td>
<td>sustaining mucosal atrophy</td>
<td>eosinophils recruited to mucosa</td>
<td>smoldering mucosal damage via EGP</td>
<td>de novo PAF synthesis</td>
</tr>
<tr>
<td>mucosal breach by flora</td>
<td>progressing mucosal necrosis via EGP</td>
<td>abundant flora</td>
<td>episodic mucosal breach by flora</td>
<td>TLR4 expression</td>
</tr>
<tr>
<td>fulminant mucosal breach by flora</td>
<td>aggressive feeding</td>
<td>variable mucosal breach by flora</td>
<td>skewed flora</td>
<td>activation of TLR4 &amp; apoptosis</td>
</tr>
<tr>
<td>23 w</td>
<td>28 w</td>
<td>32 w</td>
<td>23 w</td>
<td>28 w</td>
</tr>
</tbody>
</table>
## Reports of NEC and IgE CMPA

<table>
<thead>
<tr>
<th>Author</th>
<th>Details</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coviello, C 2012</td>
<td>Twins with IgE-mediated CMPA. T1 - 2 episodes of proctocolitis, on MBM</td>
<td>+ve RAST + eosinophilia</td>
</tr>
<tr>
<td></td>
<td>T2 - 2 NEC-like episodes in response to BMF introduction</td>
<td>PI, +ve RAST, eosinophilia</td>
</tr>
<tr>
<td>Srinivasan, P 2010</td>
<td>Preterm infant with 3 episodes of “allergic enterocolitis” secondary to BMF (2) and MBM (1).</td>
<td>PI, blood PR, Eosinophilia</td>
</tr>
</tbody>
</table>

PI = pneumatosis intestinalis
Summary

- 50% of surgical NEC occurred within a week of exposure to CMP
- Case studies show NEC may be directly caused by CMP
- CMPA may mimic NEC
  - In gastroschisis
  - In preterm infants
- CMP sensitisation seen in NEC
Hypotheses

1. CMP products may cause NEC via a non-IgE mediated CMPA mechanism

2. NEC in breast-fed babies may occur from maternal ingestion of CMP

3. Avoidance of CMP products (including EHF) may dramatically reduce the incidence of surgical NEC (and other GI dysfunction) in the preterm