Microbes, diet and host: how do they interact in newborn piglets?

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NEOMUNE

Early milk and microbiota to support immunity, gut and brain development

The NEOMUNE centre is a research platform aiming to improve the basic biology and clinical care of newborn infants, particular those born with developmental problems.

We hypothesize that diet and gut microbiota interventions during the first weeks of life promotes immunity, gut and brain maturation, both short and long term. Studies in newborn infants are coupled with studies in newborn animals (piglets, mice).
Variation in maturity at birth?

Optimal timing:
- 118d
- 116d
- 113d
- 115d

Large litters
Preterm Pig Intensive Care Unit
- to help answer difficult questions!

25 incubators
Respiratory support
Temp./moisture control
Low microbe (germfree)
Parenteral/enteral nutrition
24 hour camera surveillance
Nutrition

Microbiota

Immunity
Main risk factors of necrotizing enterocolitis (NEC):
Prematurity, formula nutrition and gut colonization
Feeding milk replacer under germ free conditions

Trophic effects on the intestine in response to enteral nutrition. No pathological changes.

# Treatment groups

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>IA anti</th>
<th>PO anti</th>
<th>Control</th>
<th>Bacteria targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>30 mg x kg x 3 daily</td>
<td>30 mg x kg x 3 daily</td>
<td></td>
<td>Gram + (-)</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>2,5 mg x kg x 2 daily</td>
<td>2,5 mg x kg x 2 daily</td>
<td></td>
<td>Gram – (+), aerobes, mycoplasma</td>
</tr>
<tr>
<td>Mitronidazole</td>
<td>10 mg x kg x 3 daily</td>
<td>10 mg x kg x 3 daily</td>
<td></td>
<td>Anaerobes</td>
</tr>
<tr>
<td>Saline</td>
<td></td>
<td></td>
<td>2 mL x 3 daily</td>
<td>None</td>
</tr>
</tbody>
</table>

Jensen et al. 2013, Am. J. Physiol
Reduced incidence, severity and gut permeability

Jensen et al. 2013, Am. J. Physiol
Markedly reduced CFU and SCFA, MEANS+SEM

Jensen et al. 2013, Am. J. Physiol
Direct infusion of lactose or MDX in the jejunum (Burrin & Stoll)
NEC incidence

Lactose: 3/11 (27%) vs. Maltodextrin: 10/11 (91%)

P < 0.001

Thymann et al. Am. J. Physiol., 2009
## Slow progression of enteral feeds in preterm pigs

<table>
<thead>
<tr>
<th>Total Parenteral Nutrition</th>
<th>TPN</th>
<th>Minimal Enteral Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infant Formula</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bovine Colostrum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral Nutrition</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>d1</th>
<th>d2</th>
<th>d3</th>
<th>d4</th>
<th>d5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN volume (ml/kg/d)</td>
<td>16</td>
<td>32</td>
<td>48</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Total fluid</td>
<td>72</td>
<td>96</td>
<td>144</td>
<td>144</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cessarian section ~90% gestation</th>
<th>Sacrifice &amp; Sampling</th>
</tr>
</thead>
</table>
Gut responses

- TPN ($n=6-14$)
- Infant Formula (IF, $n=8-15$)
- Bovine Colostrum (BC, $n=7-13$)

**NEC**

- TPN: 15%
- IF: 60%
- BC: 0%

**Gut permeability**

- Lac/Man-ratio: TPN < IF < BC

**Diarrhea**

- % of animals: TPN < IF < BC

**IL-8**

- TPN < IF < BC

**Lactose digestion**

- % of animals: TPN < IF < BC

**Galactose absorption**

- % of animals: TPN < IF < BC

First nutrition after term and preterm birth
- What are the long term consequences?

Body weight (g)

- Minimal enteral for 5d
- Total parenteral for 5d

Term
- Minimal enteral for 5d
- Total parenteral for 5d

Preterm
- Minimal enteral for 5d
- Total parenteral for 5d
PCoA on day 26

(C)

PCoA – PC1 vs PC2

Preterm MEN  Preterm TPN  Term MEN  Term TPN

PhD Status Seminar 4 March 2016
Milk and Microbiota Effects on Immunity, Gut, Liver and Brain in Preterm Infants

Comparative Pediatrics and Nutrition, Univ. Copenhagen