Infant microbiome in health and disease: current understanding and future direction

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Disclosures

Support from Danone Nutricia to be at SIGNEC 2018
Agenda

1. Term infant
2. Preterm infant
3. Looking ahead
What is the Microbiome?

Micro – Small

Biome – Community that occupies a distinct environment

Microbiomes are collections of microorganisms that live together in a given environment.
Proportion of cells in the human body

MICROBIAL CELLS
~100 TRILLION
(-70-90%)

MICROBIAL GENES
~2,000,000
(-33%)

HUMAN CELLS
~30 TRILLION

HUMAN GENES
~23,000

Gaby D'Allesandro / © AMNH
Gut microbiome

Development of the gut microbiome early in life

Gut microbiome phases

Significance and explained variance of 22 microbiome covariates

Metagenomics - Species
10,602 samples
783 children

Metagenomics - Module (function)
10,602 samples
783 children

BM increases *Bifidobacterium* and delays microbiome maturation

BM increases Bifidobacterium and delays microbiome maturation

Human milk oligosaccharides (HMOs)

Macro- and Micronutrients

Water

Human Milk

Proteins

Human Milk Oligosaccharides

Lipids

Lactose

Human Milk Oligosaccharides

- Sialyllacto-N-tetraose
- Lactodifucotetraose
- 3' and 6'Sialyllactose
- 3-Fucosyllactose
- Lacto-N-(Neo)tetraose
- Lacto-N-fucopentaose
- 2'-Fucosyllactose

Lactose

The largest nonwater component of breast milk, lactose is digested by the baby. It is also a fundamental building block of the larger oligosaccharides found in breast milk.

2'-fucosyllactose

This oligosaccharide may fight cholera, E. coli, campylobacter infection and other pathogens in the gut.

3'-sialyllactose

By changing the outer landscape of cells that line the gut, 3'SL makes it difficult for troublesome E. coli bacteria to bind and linger there, lab tests show.

Disialyllacto-N-tetraose

Studies in neonatal rodents show that DSLNT may help prevent a deadly condition common in premature infants called necrotizing enterocolitis.

Galactose Glucose Fucose N-acetylglucosamine N-acetylneuraminic acid

Bifidobacterium growth assays

Epidemiological association of breast milk with later life disease

Allergy - 117 study meta-analysis

<table>
<thead>
<tr>
<th>Grouping</th>
<th>No.</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Age 0–2 years</td>
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<td></td>
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<tr>
<td>Any duration BF</td>
<td></td>
<td></td>
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<tr>
<td>Ever vs. never</td>
<td>5</td>
<td>0.65 (0.51, 0.82)</td>
</tr>
<tr>
<td>≥3 vs. &lt;3 months</td>
<td>5</td>
<td>0.59 (0.50, 0.70)</td>
</tr>
<tr>
<td>≥6 vs. &lt;6 months</td>
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<td>0.61 (0.50, 0.74)</td>
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<tr>
<td>≥3 vs. &lt;3 months</td>
<td>6</td>
<td>0.62 (0.51, 0.74)</td>
</tr>
<tr>
<td>≥6 vs. &lt;6 months</td>
<td>3</td>
<td>0.69 (0.58, 0.81)</td>
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<tr>
<td>Age 3–6 years</td>
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<tr>
<td>Any duration BF</td>
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<tr>
<td>Ever vs. never</td>
<td>12</td>
<td>0.79 (0.68, 0.91)</td>
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<tr>
<td>≥3 vs. &lt;3 months</td>
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<td>0.84 (0.76, 0.92)</td>
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<tr>
<td>≥3 vs. &lt;3 months</td>
<td>12</td>
<td>0.81 (0.59, 1.11)</td>
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<tr>
<td>≥6 vs. &lt;6 months</td>
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<td>Age ≥7 years</td>
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<td>Ever vs. never</td>
<td>25</td>
<td>0.86 (0.77, 0.96)</td>
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<td>≥3 vs. &lt;3 months</td>
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<td>≥6 vs. &lt;6 months</td>
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<tr>
<td>≥3 vs. &lt;3 months</td>
<td>6</td>
<td>0.73 (0.39, 1.36)</td>
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<td>0.68 (0.37, 1.24)</td>
</tr>
</tbody>
</table>

Obesity – 15,253 children age 9-14 years old

<table>
<thead>
<tr>
<th>Breast-feeding duration</th>
<th>All</th>
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<tbody>
<tr>
<td>Overweight vs. normal weight, adjusted for age, sex, and Tanner stage (n = 13,163)†</td>
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<tr>
<td>&gt;9 months</td>
<td>0.63 (0.50–0.78)</td>
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<tr>
<td>7–9 months</td>
<td>0.78 (0.61–0.99)</td>
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<tr>
<td>4–6 months</td>
<td>0.78 (0.62–0.97)</td>
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<tr>
<td>1–3 months</td>
<td>0.97 (0.77–1.22)</td>
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<tr>
<td>&lt;1 month</td>
<td>1.36 (1.02–1.82)</td>
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<tr>
<td>Never breast-fed</td>
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<tr>
<td>Overweight vs. normal weight, adjusted for age, sex, Tanner stage, and maternal and child characteristics (n = 12,281)‡</td>
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<tr>
<td>&gt;9 months</td>
<td>0.79 (0.62–1.00)</td>
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<td>7–9 months</td>
<td>0.95 (0.73–1.24)</td>
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<tr>
<td>4–6 months</td>
<td>0.88 (0.68–1.12)</td>
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<tr>
<td>1–3 months</td>
<td>0.99 (0.77–1.28)</td>
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<tr>
<td>&lt;1 month</td>
<td>1.22 (0.89–1.68)</td>
</tr>
<tr>
<td>Never breast-fed</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Davis et al., Diabetes Care (2006)

Dogaru et al., Am J Epidemiology (2013)
1. Term infant
2. Preterm infant
3. Looking ahead
Key differences in microbiome acquisition and development

Preterm

Reduced:
- Diversity
- Stability
- *Bifidobacterium* sp.
- *Lactobacillus* sp.
- *Bacteroides* sp.

Full term

1-3 Years of age

Child

Increased:
- Klebsiella sp.
- *Staphylococcus* sp.
- *Escherichia* sp.
- *Enterococcus* sp.

Preterm infants restore diversity post-discharge from NICU

Stewart, CJ. et al., Nature Scientific Reports (2016)
Preterm microbiome and NEC

- Increased Gammaproteobacteria in infants diagnosed with NEC after day 30 of life only
  - Most NEC is diagnosed prior to day 30 of life
- Shannon diversity generally decreased in NEC

Warner, BB. et al. 2016. Lancet
Preterm microbiome and NEC

8 studies (106 NEC cases, 278 controls, 2944 samples)

- Potentially some differences between NEC and controls, but not predictive of onset

Microbiome modelling of NEC and LOS

Stewart, CJ. et al. 2016. *Microbiome*

7 NEC / 7 LOS / 28 matched controls. 747 samples
**Bifidobacterium and diversity associated with protection from NEC and LOS**

<table>
<thead>
<tr>
<th>PGCT</th>
<th>1</th>
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<tr>
<td>Bifidobacteria</td>
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</tbody>
</table>

Stewart, CJ. et al. 2016. *Microbiome*
NEC microbiome highly unstable

Stewart, CJ. et al. 2016. Microbiome
NEC vs. SIP tissue

Stewart, CJ. et al. Unpublished
Altered alpha- and beta-diversity in NEC

Stewart, CJ. et al. Unpublished
Significantly altered phyla in NEC

Stewart, CJ. et al. Unpublished
1. Term infant
2. Preterm infant
3. Looking ahead
Preterm enteroids to study host-microbiome in health and disease

Example uses
- Epithelial integrity
- Bacterial translocation
- Inflammatory responses
Collaborative neonatal trials

- **Speed of Increases in Feeds Trial**
  - *SIFT n=2804*

- **Enteral lactoferrin in Neonates**
  - *ELFIN n=2204*

- **Interactions between diet and growth outcomes**
  - *Exclusive human milk (Prolacta)*
  - *INDIGO n=50/100*
Mechanisms Affecting the Gut of Preterm Infants in Enteral feeding studies (MAGPIE)

Stool

Urine

Microbiome

VOCs

Metabolome

Immune (Transcriptome)

Salvaged blood / Resected tissue

MAGPIE n=481
Collaborative neonatal biobanks

**Great North Neonatal Biobank**
*Royal Victoria Infirmary*
~700 preterm infants  
~10,000 stool samples  
~3,000 Urine samples  
~3,000 Serum samples

**MAGPIE**
*12 UK centers*  
~500 preterm infants  
~15,000 stool samples  
~25,000 urine samples
Future Direction

Clinic
Samples

Discovery
‘Omics

Translation
Models

Clinic
Diagnostics/
Therapeutics

Samples

Multi-omic Variation

Genome
Epigenome
Transcriptome
Proteome
Metabolome

Human
Interventions
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