Role of Microbiome and Allergy Prevention

A/PROFESSOR JOHN SINN
MBBS (SYD), D PAED, DCH, M MED (CLIN EPI), FRACP
CONSULTANT NEONATOLOGIST AND INFANT ALLERGIST
THE PAEDIATRIC CENTRE
THE UNIVERSITY OF SYDNEY
ROYAL NORTH SHORE HOSPITAL

Pre- and postnatal environment

opportunity for early immuno-education and –programming

Higher rates of food sensitisation in more developed countries in Asia

Higher in Asian’s than non-Asians (p < 0.001)
Prevalence increased with length of stay in Australian
Higher in Australian-born Asians than Asian immigrants
Impact of western environment

Asian races more susceptible to “western” environmental changes

Development of the gut microbiota

Development of the Gut Microbiota in Breast Fed Infants

Early Nutrition
Infection/mother’s microbiota
Genetic background and imprinting
Mode of delivery
Preterm
Vaginal delivery
C-section
Early Colonisation
Motivation/Establishment
Succession/Development
Inoculation
But, after some first colonizers...
... a complex ecosystem establishes

80% starts as a sterile surface

Prepartal     Birth
0 - 4 Months  4 - 12 Months 12 - 36 Months

Preterm
Breast-feeding
Formula-feeding
Early nutrition
Bifidobacteria
Diverse microbiota
Bacteroides
Shed food and milk
Sterile microbiota

Cow’s milk-specific (IgE > 0.35 ku/l)

Breast-fed infants

Risk of allergic disease and sensitisation in Australia:
Higher in Asian’s than non-Asians (p < 0.001)
Prevalence increased with length of stay in Australian
Higher in Australian-born Asians than Asian immigrants
Impact of western environment

Adapted from prof. Susan Prescott
Cow’s milk-specific IgE (> 0.35 ku/l)

‘gradient’ with environmental change

0
2
4
6
8
10
12
14
16
18
20

Hong Kong
China (city)
China (rural)

% of children

Cow’s milk-specific (IgE > 0.35 ku/l)

20
18
16
14
12
10
8
6
4
2
0

Sicherer JACI 2010; 126: 1191

Prepartal
Birth
0 - 4 Months
4 - 12 Months
12 - 36 Months


B. longum
Bifidobacteria
Bacteroides
ecoli
Placental Microbiome

- 16S RNA gene sequencing microbial DNA.
- Without direct evidence of viable bacteria.
- Similarities between the placental and oral microbiome composition placental microbiome is partially established by haematogenous spread of oral microbiota.
- Mothers were supplemented from 36/40 and during breastfeeding 3/12.
- Lactobacillus rhamnosus GG.
- Bifidobacterium animalis subsp lactis Bb-12.
- Lactobacillus acidophilus La-5.
- Lactobacillus rhamnosus GG was identified in infant stools.

Suggestions from a Midwife

Decrease use of antibiotics.

Suggestions:
1. A vaginal birth in the mother's own environment is optimal for 'breeding' a healthy microbiome for the baby (Trichard, et al., 2012).
2. Minimize physical contact by care providers on the mother's vagina, perineum and the baby during birth.
3. Avoid unnecessary antibiotics during labour. If antibiotics are required consider probiotics for mother and baby following birth.
4. If the baby is born by c-section, research is currently being undertaken into the use of vaginal fluids to 'seed' c-section babies. The preliminary results are that the microbiome of newborns born by c-section is more similar to vaginally born babies. The protocol the researchers are using is:
   1. Take a piece of gauze soaked in sterile saline
   2. Hold it over a clean area and swab the mother's vagina
   3. Leave for 1 hour, remove just prior to surgery and keep in a sterile container
   4. Immediately after birth, apply the swab to the baby's mouth, face, then the rest of the body
5. If a baby is born by c-section it is even more important to encourage and support their mother to breastfeed. It may also be worth considering additional probiotic intake.

Microbiome

- Vagina Microbiome 80% lactobacillus.
- Newborns have actinobacteria, proteobacteria and Bacteroidales.
- Placenta: 320 mothers:
  - Ecoli, Bacteroides.
  - Is similar to mother's oral microbial.
- Once born the baby gets the hug skin bugs.
- Mothers who eat high fat diet have different gut flora in the baby.

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Caesarean section: Bifidobacteria

Comparison of bifidobacteria

<table>
<thead>
<tr>
<th>Days after birth</th>
<th>% of infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
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<td>50</td>
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<tr>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>90</td>
<td>0</td>
</tr>
</tbody>
</table>


Caesarean vs Normal vaginal delivery and Asthma Rates

Kaplan-Meier analysis of cumulative incidence of chronic asthma.
**Gastric pH and Gut flora**

- Mice with antacid had higher IgE and immediate skin reactivity cf to without antacid.
- In Humans had a 25% increase of allergy associated with Antacid ingestion after 3 months.
- Proton pump inhibitors: causes more pathogenic organism: Salmonella, Clostridia.

**Intestinal Microbiota in Allergic and Non-allergic Children**

- Allergic children have altered microbiota.
- Differences precede onset of allergic disease.
- Lower counts of bifidobacteria and enterococci at 1-12/12.
- Higher counts of clostridia in first weeks and at 3 months.
- More often colonised with staphylococcus at 6/12.

**Oils for Eczema??**

1. Almond Oil
2. Hemp Seed Oil
3. Evening Primrose Oil
4. Kukui Nut Oil
5. Carrot Oil
6. Savillower Oil 14. Peach Kernel Oil
7. Sesame Oil (Sesamum indicum) – Frequently used in Asian cooking. Sesame seed oil is high in vitamin A, B and E as well as calcium, magnesium and phosphorus. This fragrant oil is also used in various cosmetic preparations (including shampoos, sunscreens, soaps) and is used for dry eczema thanks to its skin-softening properties.
8. Wheatgerm Oil
9. Walnut Oil

**Importance oral exposure**

- Eg topical creams with any food oils and proteins
- Bleach bath

**Immuno-modulation factors: Potential Good Bugs**

- Lactobacillus GG or Rhamnosus
- Allergy prevention
- L. Reuteri
- Celic
- L. Fermentus / Salivarius
- Mastitis
- L. paracasesi: obesity
- B. Breve
- Breast milk probiotic; allergy
- Inforan: L. acidophilus / B. Bifidum: NEC
- PROPREM: ABC: 8 infants, S. thermophilus, L lactis: NEC
- Saccharomyces boulardii, Lacidophilus and B bifidum: Diarrhoea
Probiotics and Prebiotics Modulate the Intestinal Microbiota and Immune Responses

Probiotics

Prebiotics

Healthy microbiota

Interaction with PRR

SCFA epigenetic modification

Modulation of immune responses

• Epithelial integrity
• IgA secretion
• Treg, Th1/Th2 activity

Treg

Th1

Th2

Allergic disease

Eczema Infancy

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of subjects (studies)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal allergen avoidance during pregnancy</td>
<td>334 (2)</td>
<td>1.01 (0.51, 1.79)</td>
</tr>
<tr>
<td>Maternal allergen avoidance during lactation</td>
<td>26 (1)</td>
<td>0.73 (0.32, 1.64)</td>
</tr>
<tr>
<td>Partially hydrolysed formula versus cow’s milk formula</td>
<td>1245 (8)</td>
<td>0.99 (0.84, 1.17)</td>
</tr>
<tr>
<td>Extensively hydrolysed formula versus cow’s milk formula</td>
<td>1727 (2)</td>
<td>0.94 (0.85, 1.05)</td>
</tr>
<tr>
<td>Extensively versus partially hydrolysed formula</td>
<td>3665 (4)</td>
<td>0.89 (0.72, 1.10)</td>
</tr>
<tr>
<td>Soy formula versus cow’s milk formula</td>
<td>571 (1)</td>
<td>1.62 (0.95, 2.71)</td>
</tr>
<tr>
<td>Prebiotics</td>
<td>1218 (4)</td>
<td>0.96 (0.94, 0.97)</td>
</tr>
<tr>
<td>Prebiotics</td>
<td>1911 (13)</td>
<td>0.79 (0.68, 0.91)</td>
</tr>
</tbody>
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Prebiotic Concept

- Non digestible food ingredients that selectively stimulate the growth of non-pathogenic bacteria in the large intestine.
- Breast milk contains prebiotics.

Prebiotics

- Beneficial Bacteria
- Lactobacillus Rhamnosus for allergy

Probiotics

- Indigestible fibre that support the growth of Probiotics
- The 3rd largest component of Breast milk by dry weight

Effect of Breastfeeding On Gut Flora

Development of Intestinal microflora in a breast-fed and a formula-fed infant in the first 30 days after birth.25

% microbiota abundance

Breast-fed infant

Formula-fed infant

Adapted from Harmsen et al., 2000. Study of breast-fed and formula-fed infants, over 21 days after birth.24
Prebiotics in infants for prevention of allergic disease and food hypersensitivity

DAVID A OSBORN, JOHN KH SINN
ROYAL PRINCE ALFRED HOSPITAL
ROYAL NORTH SHORE HOSPITAL
AUSTRALIAN SATELLITE OF THE COCHRANE NEONATAL REVIEW GROUP, AUSTRALIA

Prebiotic versus no prebiotic: Infant eczema incidence

- **4 trials, 1218 infants**
- **RR = 0.46, 95% CI 0.28, 0.77; p=0.03**
- Heterogeneity: $I^2 = 34\%$

Subgroup analysis: Infant risk of allergic disease

- **Infant asthma incidence**
  - Test subgroup differences: $P = 0.07$, $I^2 = 69\%$
  - RR 0.37 95%CI 0.14, 0.96
  - RR 1.07 95%CI 0.56, 2.06

Established PREbiotics

- Breast Milk oligosaccharides
- Milk 20 gm/l in colostrum & 12-14 gm/l in mature milk.
- Polydextrose
- Inulin **Wheat, banana, onions, garlic, leek, chicory.**
- FOS (Fructo-oligosaccharides or oligofructose) **plants.**
- GOS (Galacto-oligosaccharides) **milk.**
- Lactulose

*(Journal of the American Dietetic Association, 2008)*

POSTbiotics

- Short chain fatty acids (SCFAs) are the products of colonic bacterial degradation of unabsorbed starch
- Acetate, Propionate, and Butyrate and Lactic acid.

  *Colonocyte (Proliferation / Differentiation)*
  *& Function (Tight Colonic Junction / Inflammatory Suppression).*

SCFAs help improve Water & Electrolyte Absorption

- SCFA facilitate absorption of water and electrolytes
- Acetate increases colonic blood flow and enhances ileal motility.
SCFAs support the critical Gut mucosal barrier: Keeping Gut integrity

- Butyrate
  - provides fuel for colonic epithelial cells,
  - Help heal
  - LOW Fiber Diet → low SCFA → high occurrence of colonic disorders.

SCFAs effects in peanut allergy
200mM acetate, 100mM butyrate, 100mM propionate for 3 weeks in drinking water

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Probiotic versus no probiotic: Infant eczema: 13 trials, 1911 infants

Heterogeneity: $P = 0.37; I^2 = 8\%$
Test for overall effect:
$P = 0.001$
Eczema – Probiotic containing L. rhamnosus versus other probiotic

Test for subgroup differences: P = 0.18, I² = 45.3%
RR 0.68 95%CI 0.53, 0.86
RR 0.83 95%CI 0.70, 1.00

Synbiotic versus no synbiotic: Infant allergy, eczema, atopic

Infant eczema: NNTB 17 [95%CI 12, >100], p=0.04

Summary: Prevention

- Allergy Prevention
- Breast feeding
- Prebiotics/probiotics
- Hydrolysed formula
- Vit D

Take Home message

- Gut flora important to regulate the immune system not to overreact and become allergic to food or aerallergen
- Ensuring good microbiome is the key for prevention of allergy and also childhood infections
- Breast Fed as long as possible
- Infant formula with prebiotic or probiotics
- Supplementation with probiotics during pregnancy, lactation and to infant as per WAO

Food sensitisation

- 17 trials (2947 infants)
  - combined pre- and postnatal probiotic treatment reduced the risk of (any) sensitization (RR 0.78; 95% CI 0.66–0.92)
  - Food sensitization (RR 0.77; 95% CI 0.61–0.98).
What to recommend

- Family history of allergy:
  - For mothers:
    - Probiotic during 3rd trimester
    - Probiotics during lactation
  - For baby
    - If not breast fed:
      - Probiotics and prebiotics (synbiotics)
  - For LSCS or Antibiotics for mother
  - Consider probiotics for mother and Synbiotics for baby
  - For eczema children: risk factor for more allergy
    - Lactobacillus rhamnosus
  - For infant antibiotics
    - Probiotics to prevent diarrhoea and change of gut microbiome

The Paediatric Centre St Leonards

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