Disclosure Statement

Dr. Allan Walker has disclosed the information listed below. Any real or apparent conflict of interest related to the content of the presentation has been resolved.

<table>
<thead>
<tr>
<th>Organization Name</th>
<th>Affiliation/Financial Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dannon/Yakult International</td>
<td>Scientific Advisory Board</td>
</tr>
<tr>
<td>Mead Johnson Nutritional</td>
<td>Research Grant &amp; Scientific Advisory Board</td>
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UCSF 44th Annual Advances and Controversies in Clinical Pediatrics

Westin Hotel, San Francisco

May 13, 2011

Lecture title: “Breast Feeding: The Short and Long Term Effects on Infant’s and Children’s Health!”

Allan Walker, M.D.

Boston, MA

Breastfeeding and Infant/Child Health

Breastfeeding provides the infant with nutrition and forms a bond between the mother and the infant.

Breastfed infants have reduced risk of multiple age-related diseases.
**Breastfeeding and Infant/Child Health**

**Lecture outline**
- overall philosophy - justification
- clinical disease protection (short term)
- clinical disease protection (long term)
- summary and conclusions

---

**Overall Philosophy**: Breast milk provides a protective link from mother to newborn in the extrauterine environment and helps to prevent both short term and long term clinical diseases.
Lecture outline

- overall philosophy – justification
- composition – as needed for age
- intestinal host defense
- anti-inflammation

Composition – as needed for age

- growth factors
- phagocytosis
- pIgA

Intestinal Cell Turnover

Adult

Neonate
**Breastfeeding and Infant/Child Health**

*Colostrum effect on intestinal epithelium maturation*

![Diagram showing Colostrum and Postcolostrum]

**Breastfeeding and Infant/Child Health**

*Gastrointestinal Development*

![Graph showing HTdR Incorporation into DNA (CPM x 10^-4) vs. % (V/V)]

**Breastfeeding and Infant/Child Health**

*EGF levels vs. age*

![Graph showing EGF concentration in milk (ug/L) vs. Days of Lactation]
Breastfeeding and Infant/Child Health

PHAGOCYTIC INDEX

Preterm Milk Leukocytes
Term Milk Leukocytes


p < 0.001

Breastfeeding and Infant/Child Health

Elevated IgA concentration in milk produced by mothers delivered of preterm infants.
Gross SJ, Buckley RH, Wahl SS, Macklinn DC, Davis RE, Fain RG.

Breastfeeding and Infant/Child Health

Lecture outline

• overall philosophy – justification
• composition – as needed for age
• intestinal host defense
• anti-inflammation
Breastfeeding and Infant/Child Health

Intestinal host defense

- secretory IgA
- enteromammary system
- oligosaccharides
- oral tolerance

Breastfeeding and Infant/Child Health

MATURE

IMMUNE RESPONSE TO INTESTINAL ANTIGEN --
LOCAL IgA RESPONSE

LUMEN
MUCOSA
SUBMUCOSA

Breastfeeding and Infant/Child Health

IMMATURE

IMMUNE RESPONSE TO INTESTINAL ANTIGEN --
ABSENT LOCAL IgA RESPONSE: SIgA DEFICIENCY

LUMEN
MUCOSA
SUBMUCOSA

Breastfeeding and Infant/Child Health
Breastfeeding and Infant/Child Health

**sIgA vs. newborn age**

Percent of infants with detectable salivary γA

Age in days

Breastfeeding and Infant/Child Health

**Concentration of sIgA in breastmilk**

<table>
<thead>
<tr>
<th>Days</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

Breastfeeding and Infant/Child Health

**Intestinal host defense**

- secretory IgA
- enteromammary system
- oligosaccharides
- oral tolerance
Intestinal host defense

- secretory IgA
- enteromammary system
- oligosaccharides
- oral tolerance
Breastfeeding and Infant/Child Health

Oligosaccharides in breast milk (b.m.) vs. age

Prebiotic effect

Intestinal host defense

- secretory IgA
- enteromammary system
- oligosaccharides
- oral tolerance
Breastfeeding and Infant/Child Health

Mature immune response to intestinal antigens

Oral tolerance

LUMEN

MUCOSA

SUBMUCOSA

Breastfeeding and Infant/Child Health

IMMATURE IMMUNE RESPONSE TO INTESTINAL ANTIGENS—
SYSTEMIC ANTIBODY RESPONSE: IgE ALLERGY, IgE-COMPLEX DISEASE

Breastfeeding and Infant/Child Health

Systemic response to antigens

<table>
<thead>
<tr>
<th>Serum IgE (U/mL)</th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
</tr>
</tbody>
</table>

1 - Formula fed - milk proteins
II - Formula fed - soy proteins
III - Breast fed (3 mo) - formula milk proteins

Eastham, J Paediatric, 1978
Breastfeeding and Infant/Child Health

Lecture outline
- overall philosophy – justification
- composition – as needed for age
- intestinal host defense
- anti-inflammation

Breastfeeding and Infant/Child Health

Inflammatory response

Anti-inflammatory effects of breast milk
- general
- trophic factors - ex. cortisone
- regulatory cytokines - TGFβ
- omega-3 fatty acids
Breastfeeding and Infant/Child Health

Toll-like Receptor Signal Transduction Pathways

<table>
<thead>
<tr>
<th>Immune response gene</th>
<th>IL-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammals</td>
<td></td>
</tr>
<tr>
<td>LPS</td>
<td></td>
</tr>
<tr>
<td>LBR</td>
<td></td>
</tr>
<tr>
<td>TLR4</td>
<td></td>
</tr>
<tr>
<td>IL-1R</td>
<td></td>
</tr>
<tr>
<td>NIK</td>
<td></td>
</tr>
<tr>
<td>TRAF6</td>
<td></td>
</tr>
<tr>
<td>IRAK</td>
<td></td>
</tr>
<tr>
<td>MyD88</td>
<td></td>
</tr>
<tr>
<td>NFκB</td>
<td></td>
</tr>
<tr>
<td>IκB</td>
<td></td>
</tr>
<tr>
<td>DEGRADATION</td>
<td></td>
</tr>
</tbody>
</table>

Breastfeeding and Infant/Child Health

Effect of colostrum on expression of IL-8 and TLR4 in fetal ileal xenografts

Fold change in mRNA

Breastfeeding and Infant/Child Health

Bacterial Enterocyte Cross-Talk in the Developing Gut

Human MMIR Factors vs. TNF

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>IL-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>0</td>
</tr>
<tr>
<td>TNF</td>
<td>25%</td>
</tr>
<tr>
<td>TGFβ1</td>
<td>43%</td>
</tr>
<tr>
<td>EGF</td>
<td>20%</td>
</tr>
</tbody>
</table>

Claud and Walker, Ped Res 2003;53:419
Omega 3 fatty acids and inflammation

Requena et al. (unpublished data)

Effect of DHA on IL-1β-induced IL-6 production in fetal intestinal epithelial cells

Breastfeeding and Infant/Child Health

Lecture outline
- overall philosophy - justification
- clinical disease protection (short term)

Clinical disease
- fortuitous protection
  - cretinism
  - acrodermatitis enteropathica
Breastfeeding and Infant/Child Health

Mitigation of cretinism by breast-feeding.
Bode HH, Vanjonack WJ, Crawford JD.
Pediatrics 1978; 62:13-6

Breastfeeding and disease prevention

Zinc binding: a difference between human and bovine milk.
Eckhardt CB, Shum APF, Duncan JR, Harley JS.
Science 1977; 195:789-90

Clinical disease protection (short term)
- infantile diarrhea
- necrotizing enterocolitis
- eczema
Breastfeeding and Infant/Child Health

**Breast feeding and diarrhea**

*(developing countries)*

Occurrence of and death resulting from diarrhea in relation to mode of feeding from January 1973 to April 1977

<table>
<thead>
<tr>
<th>Mode of feeding</th>
<th>Diarrhea Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
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<tr>
<td>Breast-fed</td>
<td>9,622</td>
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<tr>
<td>Mixed-fed</td>
<td>611</td>
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<tr>
<td>Formula-fed</td>
<td>2,603</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mode of feeding</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Breast-fed</td>
<td>38</td>
</tr>
<tr>
<td>Mixed-fed</td>
<td>0</td>
</tr>
<tr>
<td>Formula-fed</td>
<td>38</td>
</tr>
</tbody>
</table>


Breastfeeding and Infant/Child Health

**Postnatal infections**

![Graph showing percent of children free of diarrhea vs. days postpartum]


Breastfeeding and Infant/Child Health

**Campylobacter diarrhea**

![Bar chart showing episodes of Campylobacter diarrhea per child-year by age in months]

Breastfeeding and Infant/Child Health

Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy.

Duijts L, Jaddoe VW, Hofman A, Moll HA.
Generation R Study Group, Rotterdam, Netherlands.

*Pediatrics. 2010;126:e18-25*

<table>
<thead>
<tr>
<th>Duration of breastfeeding, mo</th>
<th>Protection - 1st 6 months</th>
<th>Protection - 1-12 months</th>
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<tbody>
<tr>
<td>&lt; 4</td>
<td></td>
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<tr>
<td>4-6</td>
<td></td>
<td></td>
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<tr>
<td>≥ 6</td>
<td></td>
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</table>

Lower Respiratory Infection

Gastrointestinal Infection

Breathing easier with breastmilk.

Puddington L, Matson A.

*Nat Med. 2008;14(2):116-8*

Breastfeeding and Infant/Child Health

Meta-Analysis- breastfeeding and NEC

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>#Pts</th>
<th>0.01</th>
<th>0.02</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>5</th>
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<th>30</th>
<th>50</th>
<th>100</th>
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<tr>
<td>Cross</td>
<td>1983</td>
<td>67</td>
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<tr>
<td>Tyson</td>
<td>1983</td>
<td>81</td>
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<td>Lucas</td>
<td>1984</td>
<td>162</td>
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<td>Schanler</td>
<td>2005</td>
<td>166</td>
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<tr>
<td>Overall</td>
<td>476</td>
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</tr>
</tbody>
</table>

Favors breast milk

Favors control

Breastfeeding and Infant/Child Health

Allergens and breastfeeding

Puddington L, Matson A.

*Sut Med. 2008;14(2):116-8*
Breastfeeding and Infant/Child Health

Transforming growth factor-beta and interleukin-10 in breast milk and development of atopic diseases in infants.

Rigotti E, Piacentini GL, Ross M, Pignati R, Bonini AL, Peroni DG.
Department of Pediatrics, University of Verona, Verona, Italy.

Clin Exp Allergy. 2006;36:614-8

TGF – β breast milk

Colostrum Milk
Allergic mothers

Non-allergic mothers

Breastfeeding and Infant/Child Health

Breastfeeding of allergic infants.

Isolauri E, Tahvanainen A, Peltola T, Arvola.
Department of Pediatrics, University of Turku, Finland.


Breastfeeding and Infant/Child Health

Lecture outline

- overall philosophy - justification
- clinical disease protection (short term)
- clinical disease protection (long term)
Breastfeeding and Infant/Child Health

Clinical disease protection (long term effects)

- obesity
- type II diabetes
- allergy
- autoimmune disease
- cardiac risk factors
- cognitive function

Mean weight-for-age z-scores of healthy breastfed infants relative to the WHO standards and the CDC 2000 charts

Breastfeeding and Infant/Child Health

Risk of Overweight Among Adolescents Who Were Breastfed as Infants

Gillman MW, Rifas-Shiman SL, Camargo, Jr. CA, Berkey CS, Frazier L, Rockett HRH, Field AE, Colditz GA

Breastfeeding and obesity
**Breastfeeding and Infant/Child Health**

Evidence on the long-term effects of breastfeeding: Systematic reviews and meta-analyses

Horta BL, Bahl R, Martines JC, Victora CG

Breastfeeding and adult obesity

Duration of breast feeding (months)

Odds ratio of overweight

- 0.2
- 0.4
- 0.6
- 0.8
- 1.0
- 1.2

World Health Organization 2007

---

**Breastfeeding and Infant/Child Health**

Does breastfeeding influence risk of type 2 diabetes in later life?

A quantitative analysis of published evidence.

Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG

Division of Community Health Sciences, St George's, University of London, London

Breast feeding and type II diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds of type 2 diabetes</th>
<th>Effect size</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin, 71y (11)</td>
<td>0.61 (0.44, 0.85)</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Fall, 64y (10)</td>
<td>0.56 (0.23, 1.38)</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>Rich-Ewards, 59y (14)</td>
<td>0.51 (0.28, 0.93)</td>
<td>29.6</td>
<td></td>
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<tr>
<td>Martin, 45-59y (18)</td>
<td>0.46 (0.23, 0.93)</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>Ravelli, 50y (6)</td>
<td>0.25 (0.63, 1.20)</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Pettitt, 10-39y (21)</td>
<td>0.11 (0.08, 0.13)</td>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td>Young, 13y (22)</td>
<td>0.06 (0.23, 1.48)</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.41 (0.46, 0.30)</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

---

**Breastfeeding and Infant/Child Health**

Breastfeeding in relation to asthma, lung function, and sensitization in young school children

Kull I, Melin E, Alm I, Hallberg J, Svartengren M, van Hage M, Pershagen G, Wickman M, Bergström A

Institute of Environmental Medicine, Karolinska Institute, Sweden


Exclusive breast-feeding (≥4 months) and asthma

<table>
<thead>
<tr>
<th>Exclusive breast-feeding</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 y</td>
<td>1.0</td>
</tr>
<tr>
<td>1 yr</td>
<td>1.1</td>
</tr>
<tr>
<td>2 yr</td>
<td>1.2</td>
</tr>
<tr>
<td>Overall effect 0-8 y</td>
<td>1.3</td>
</tr>
</tbody>
</table>

---

**Breastfeeding and Infant/Child Health**

Breast-feeding in relation to asthma, lung function, and sensitization in young school children

Kull I, Melin E, Alm I, Hallberg J, Svartengren M, van Hage M, Pershagen G, Wickman M, Bergström A

Institute of Environmental Medicine, Karolinska Institute, Sweden

Effect of breastfeeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies.

Akobeng AK, Ramanan AV, Buchan I, Heller RF.
Department of Paediatric Gastroenterology, Booth Hall Children's Hospital, Central Manchester, UK.

Arch Dis Child. 2006;91(1):39-43

Breastfeeding and coeliac disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters et al</td>
<td>0.46 (0.27, 0.78)</td>
</tr>
<tr>
<td>Faith Magnuson et al</td>
<td>0.35 (0.17, 0.66)</td>
</tr>
<tr>
<td>Inarsson et al</td>
<td>0.50 (0.40, 0.64)</td>
</tr>
<tr>
<td>Anchor et al</td>
<td>1.54 (0.27, 10.56)</td>
</tr>
<tr>
<td>Combined (fixed)</td>
<td>0.48 (0.40, 0.59)</td>
</tr>
</tbody>
</table>

Breastfeeding and infant/child health

Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis.

Klement E, Cohen BV, Barton J, Joseph A, Rad S.
Koren Institute of Veterinary Medicine, the Hebrew University of Jerusalem, Rehovot, Israel.


Breastfeeding and Crohn's disease

Pooled OR of all studies

Breastfeeding and infant/child health

Infant feeding and blood cholesterol: a study in adolescents and a systematic review.

Owen CG, Whincup PH, Odoki K, Gilg JA, Cook DG.
Department of Public Health Sciences, St George's Hospital Medical School, Cranmer Terrace, London.


Breastfeeding and cholesterol levels
Breastfeeding and Infant/Child Health

**Breastfeeding and cognitive development: a meta-analysis.**
Anderson JW, Johnstone BM, Remley DT.
Metabolic Research Group, Veterans Affairs Medical Center.

**Breastfeeding vs. formula and cognitive development**

<table>
<thead>
<tr>
<th>Study</th>
<th>Formula-fed Benefit</th>
<th>Breast-fed Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florey et al (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temboury et al (16)</td>
<td></td>
<td></td>
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<tr>
<td>Rogan and Gladen (13)</td>
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<tr>
<td>Lucas et al (12)</td>
<td></td>
<td></td>
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<tr>
<td>Jacobson and Jacobson (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doyle et al (11)</td>
<td></td>
<td></td>
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<tr>
<td>Morrow - Tlucak et al (8)</td>
<td></td>
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</tr>
<tr>
<td>Morley et al (7)</td>
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<td></td>
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<tr>
<td>Ounsted et al (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fergusson et al (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roger (3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Breastfeeding and Infant/Child Health**

**Maternal diet**
- fat content determined by maternal diet
  - omega-3 fatty acids
  - trans fatty acids

* very important

**Trans Fatty acids in milk produced by women in the United States**

Mosley EE, Wright AL, McGuire MK, McGuire MA.
Department of Animal and Veterinary Science, University of Idaho, Moscow, ID.

**Values (% by wt of total FAs)**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Values (% by wt of total FAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study</td>
<td>Arizona (n = 33)</td>
<td>2.3 (2.5 - 3.8)</td>
</tr>
<tr>
<td>Chen et al (17)</td>
<td>Canada (n = 190)</td>
<td>2.3 ± 0.3 (0.1 - 17.2)</td>
</tr>
<tr>
<td>Dolezal et al (21)</td>
<td>Czech Republic (n = 33)</td>
<td>4.1 ± 1.9 (0.9 - 9.8)</td>
</tr>
<tr>
<td>Precht and Molkentin (18)</td>
<td>Germany (n = 40)</td>
<td>5.8 ± 1.0 (2.4 - 6.0)</td>
</tr>
<tr>
<td>Kolevko et al (19)</td>
<td>Nigeria (n = 10)</td>
<td>1.2 (0.8 - 10.2)</td>
</tr>
<tr>
<td>Kolevko et al (20)</td>
<td>Germany (n = 15)</td>
<td>4.4 (2.2 - 6.8)</td>
</tr>
<tr>
<td>Chen et al (20)</td>
<td>Chongqing, China (n = 33)</td>
<td>4.3 ± 0.06 (NA)</td>
</tr>
<tr>
<td>Chen et al (20)</td>
<td>Hong Kong, China (n = 51)</td>
<td>0.87 ± 0.31 (NA)</td>
</tr>
<tr>
<td>Bonilla et al (34)</td>
<td>Spain (n = 38)</td>
<td>NA (1.2 - 4.8)</td>
</tr>
</tbody>
</table>
Breastfeeding and Infant/Child Health

Lecture outline
- overall philosophy - justification
- clinical disease protection (short term)
- clinical disease protection (long term)
- summary and conclusions

Breastfeeding and Infant/Child Health

Summary and conclusions
- breastmilk provides a protective link from mother to newborn
- passive protection is provided to infant as needed by changing breastmilk factors
- breastmilk can actively stimulate immaturities in neonatal host defenses
- provides short and long term clinical disease protection