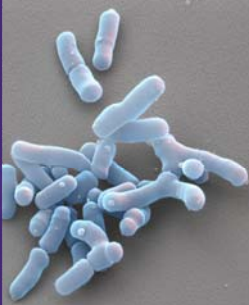
  
NUTRICIA LEARNING CENTER

**Probiotics, Prebiotics and the Role of the Infant Intestinal Microbiota in Health and Allergic Disease**

Kelly Tappenden, Ph.D, R.D.



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NUTRICIA LEARNING CENTER

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**Learning Objectives** 

1. Discuss development of the intestinal microbiota in early life.
2. Explain dysbiosis in the early life intestinal microbiota and allergic diseases.
3. Understand the role of specific probiotics and prebiotics in pediatric nutrition.
4. Explore emerging evidence in the management of cow milk allergy.

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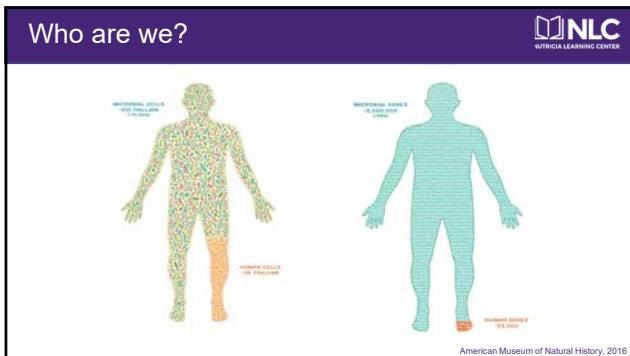
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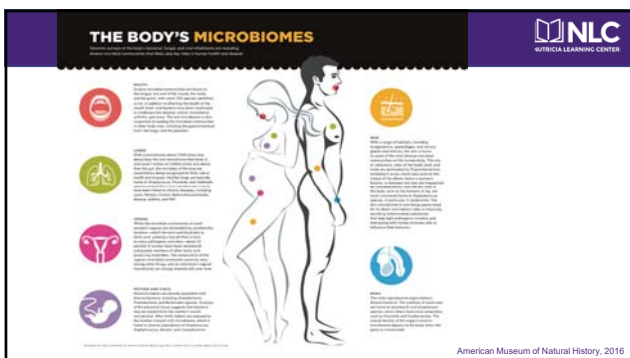
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### Functions of the Intestinal Microbiota



Functions	Mechanisms/Effects
Digestive and metabolic functions	<ul style="list-style-type: none"> <li>Vitamin production</li> <li>Fermentation of nondigestible CHO → SCFA</li> <li>Dietary carcinogens metabolism</li> </ul>
Neuronal development	<ul style="list-style-type: none"> <li>Modulation of brain gut axis during neuronal development</li> <li>Motor control and anxiety behavior</li> </ul>
Protective functions against pathogenic bacteria	<ul style="list-style-type: none"> <li>Pathogen displacement</li> <li>Nutrient competition</li> <li>Production of antimicrobial factors</li> <li>Activation of local immune response</li> <li>Contribute to the intestinal barrier function</li> </ul>
Immune development	<ul style="list-style-type: none"> <li>IgA production</li> <li>Control of local and general inflammation</li> <li>Tightening of junctions</li> <li>Induction of tolerance to foods</li> </ul>

Buccigrossi et al., Curr Opin Gastroenterol 2013, 29:31-38

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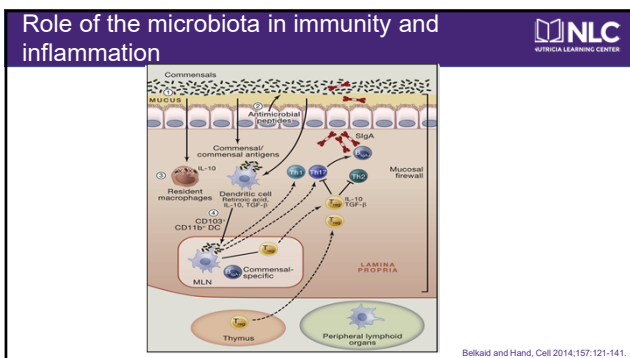
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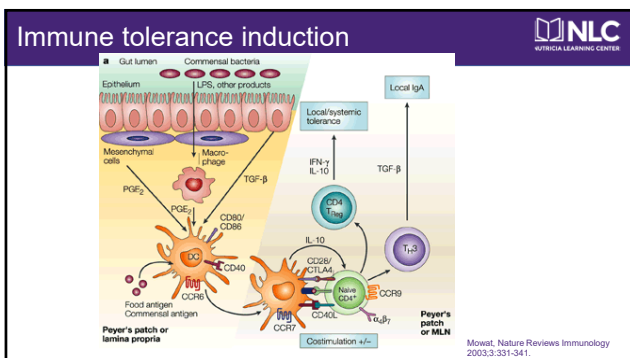
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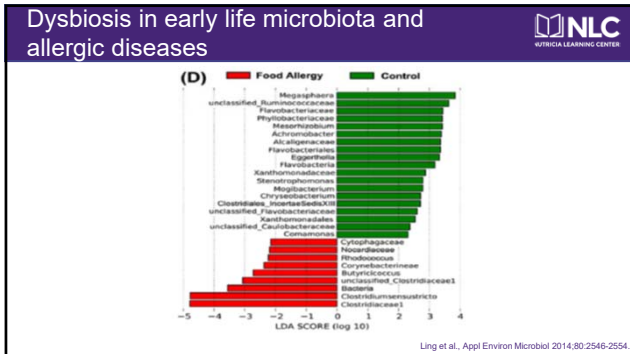
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### Dysbiosis precedes development of allergic phenotypes

Age of dysbiosis	Phenotype	Age at diagnosis	Reference
1 month	Eczema	2 years	Abrahamsson et al., JACI 2012;129:434-440.
Day 7	Eczema	12 months	Ismail et al., PAI 2012;23:674-681.
1 week	Eczema	18 months	Wang et al., JACI 2008;121:129-134.
1 week/12 months	IgE, eos, rhinitis; NOT asthma, eczema	up to 6 years	Bisgaard et al., JACI 2011; 129:646-652.
3 weeks	Asthma		Vael et al., BMC Microbiol 2011;11:68.

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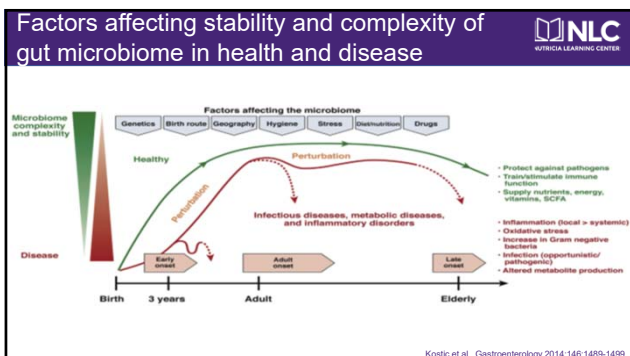
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### Microbiota: human milk vs infant formula?

- Breast-fed infants
  - stable developing microbiota
  - dominated by bifidobacteria ('bifidofactor')
  - decreased pathogens
- Formula-fed infants
  - Less stable microbiota
  - assoc with higher incidence of pathogenic infections, diarrhea, pneumonia and allergy



Harmsen et al., JPGN 2009;30:61-67

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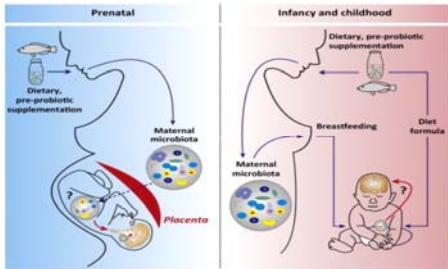
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### Microbe contact begins *in utero*



Borre et al., Trends Mol Med 2014;20:509-518

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### What's in human milk?

Human milk oligosaccharides (HMOs) are food for friendly bacteria like *Bifidobacterium infantis*. Shorter chain HMOs in particular are almost entirely consumed by this microbe.

Milk	Macro-/micronutrients	HMOs	Chain length	Proportion eaten by <i>B. infantis</i> (%)
Macro- and micronutrients	Water	HMOs	4	~100
		Proteins	5	~100
Lipids	Lactose	HMOs	6	~100
		HMOs	7	~100
Lactose	Lactose	HMOs	8	~100
		HMOs	9	~100
Lactose	Lactose	HMOs	10	~100
		Other HMOs of longer lengths	>10	~0

Petherick, Nature 2010;65:55-57

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**What is a PRObiotic?** 

- Oral probiotics are *living* microorganisms that upon ingestion in specific numbers, exert health benefits beyond those of inherent basic nutrition (sometimes also referred to as “good bacteria”).
- Mostly *Bifidobacteria* and *Lactobacilli*
- Effects are immune stimulation, anti-pathogenic, gut barrier, removal of toxic substances, providing metabolites to gut cells (Gorbach 2002; Marteu & Shanahan 2003; Mercenier 2003)
- Added value of probiotics particularly in allergic subjects (Majamaa & Isolauri 1997; Kirjavainen & Gibson, 1999; Isolauri 2001; Viljanen 2005, Weston 2005; Sitek 2006; Canani 2012)

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**What is a PREbiotic?** 

- A prebiotic is a non-digestible *food* ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one of a limited number of bacteria in the colon, and thus improves host health. (Gibson and Roberfroid,1995; Gibson et al., 2004)
- Stimulate growth of beneficial bacteria (*Bifidobacteria*, *Lactobacilli*), but not the harmful ones (Gibson, 1999)
- Prebiotic ingredients stimulate gut microbiota to be more like that of breast fed infants (Boehm 2002, 2003; Schmeitz 2003; Moro 2003; Haarman & Knol 2005)
- Produced bacterial metabolites positively influence immune system (Boehm 2004; Vos 2007)
- Reduce the incidence of allergy in the infants at risk (Aralanoglu 2008; Van Hoffen 2009)




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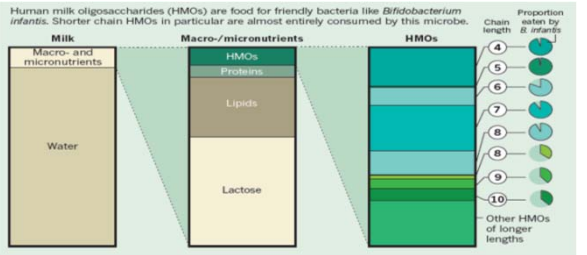
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**Human milk = the ultimate SYNbiotic!** 

Human milk oligosaccharides (HMOs) are food for friendly bacteria like *Bifidobacterium* infants. Shorter chain HMOs in particular are almost entirely consumed by this microbe.



Petherick Nature 2010.65.S5-S7

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**Synbiotics = prebiotic + probiotic** 

Can nutritional formulas be modified  
 - using a **SYNbiotic** approach -  
 to alter the intestinal microbiota and  
 improve clinical outcomes in children?

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**Selection of PRObiotic ingredients critical for management of infants with cow milk allergy** 

- Through preclinical research *Bifidobacterium breve* M-16V was specifically selected for an amino acid-based formula for its compatibility with allergy as verified in milk-allergic infants.
- Research has shown that a blend of *Bifidobacterium breve* M-16V and prebiotic short- and long-chain fructooligosaccharides can help balance the gut microbiota of food allergic infants, bringing it closer to that of healthy breastfed infants.

Hougee et al., Int Arch Allergy Immunol. 2010;151:107-17.  
 Harvey et al., Pediatr Res. 2014;75:343-51.  
 Burks et al., Pediatr Allergy Immunol. 2015;26:316-22.  
 Michaelis et al., Allergy. 2016; 71 (S102): 58

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***Bifidobacterium breve* is safe in human infants** 

- Safety of probiotics in infant formula has been well-documented with a number of studies (Moro 2002; Saavedra 2004; Knol 2005; Moro 2006; Vlieger 2009)
- *B. breve* – one of the predominant bifidobacterial species in human breast milk and in the microbiota of healthy breastfed infants
- *B. breve* is most effective probiotic strain when compared to other probiotic bacteria (anti-allergic activity), efficacy of *B. breve* tested in several clinical studies (neonates, LBW infants) (Akiyama 1994; Hattori 2003; Sato 2003; Patole 2014)
- Safety of *B. breve* has been demonstrated in *in vitro*, *in vivo* toxicity studies (Fukushima Laboratory Fukushi Japan 1992), and in a dozen clinical trials

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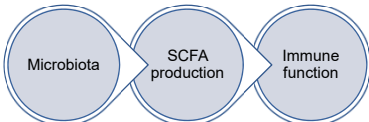
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### Studies support benefits of synbiotics associated with allergic disease



- Synbiotics prevent atopic eczema and increase resistance to infections in infants at risk of allergy (Kukkonen 2007; 2008)
- Synbiotics, including *B. breve*, support clinical improvement in infants with IgE-associated atopic dermatitis (AD) (Van der Aa 2010) and reduction of asthma-like symptoms in infants with AD (Van der Aa 2011)
- Synbiotics, including *B. breve*, reduced allergen-specific immune response and improve respiratory parameters in allergic asthmatic adults (Van de Pol 2011)



The diagram consists of three overlapping circles. The left circle is labeled 'Microbiota', the middle circle is 'SCFA production', and the right circle is 'Immune function'. Arrows point from Microbiota to SCFA production, and from SCFA production to Immune function.

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### Amino acid-based formula (AAF) with specific synbiotics aims to eliminate allergens for active management of cows milk allergy



**maximal allergen elimination**

- Hypoallergenic formula
- 100% amino acids
- 0-12 months

**helps to address underlying gut dysbiosis**

- sc-FOS / lc-FOS (9:1 ratio)  
0.63g / 100 ml  
no GOS, to avoid CMP contamination
- Bifidobacterium breve* M-16V  
10<sup>8</sup> CFU/g powder  
processed in a milk-free environment

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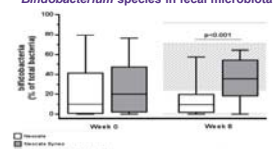
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### AAF + specific synbiotics promotes *bifidobacteria* growth and reduces *Eubacterium/Clostridia*, similar to breast fed infants

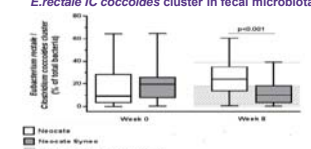
The flowchart shows a study with two groups: 'Non IgE CMA infants group' (n=71) and 'Healthy breastfed group'. The CMA group is split into 'Test product for 8 weeks' (n=35) and 'Control product for 8 weeks' (n=36). Both groups then have an 'optional' phase with 'Test product optional\*' and 'Control product optional\*'. Sampling points (T0wks, T12wks FUP, T24wks FUP) are indicated. The healthy breastfed group has 'No study product' and a note that '\*if continuation on AAF is appropriate'.

***Bifidobacterium* species in fecal microbiota**



At Week 0, the 'Test product' group (white box) has a median of approximately 20% Bifidobacterium, while the 'Control product' group (gray box) has a median of approximately 10%. At Week 8, the 'Test product' group (white box) has a median of approximately 40%, while the 'Control product' group (gray box) has a median of approximately 20%. A p-value of <math>p=0.001</math> is shown.

***E. rectale IC coccoides* cluster in fecal microbiota**



At Week 0, the 'Test product' group (white box) has a median of approximately 20% E. rectale IC coccoides, while the 'Control product' group (gray box) has a median of approximately 30%. At Week 8, the 'Test product' group (white box) has a median of approximately 10%, while the 'Control product' group (gray box) has a median of approximately 20%. A p-value of <math>p=0.001</math> is shown.

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World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): **PRE**biotics 

**Objective.** The World Allergy Organization (WAO) convened a guideline panel to develop evidence-based recommendations about the use of prebiotics in the prevention of allergy.

**Methods.** Used Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to develop recommendations (evidence up to July 2015).

**Recommendation.** Based on GRADE evidence to decision frameworks, the **WAO guideline panel suggests using prebiotic supplementation in not-exclusively breastfed infants.**

Cuello-García et al., World Allergy Organization Journal (2016) 9:1-10

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World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): **PRO**biotics 

**Recommendations.** Currently available evidence does not indicate that probiotic supplementation reduces the risk of developing allergy in children. However, considering all critical outcomes in this context, the WAO guideline panel determined that there is a likely net benefit from using probiotics resulting primarily from prevention of eczema.

The WAO guideline panel suggests:

- a) using probiotics in pregnant women at high risk for having an allergic child;
- b) using probiotics in women who breastfeed infants at high risk of developing allergy; and
- c) using probiotics in infants at high risk of developing allergy.

All recommendations are conditional and supported by very low quality evidence.

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**Conclusion** 

Nutritional strategies employing **PRO**biotics AND **PRE**biotic fiber – hence **SYN**biotics – are important for addressing dysbiosis of the developing intestinal microbiota and stimulating critical development of the immune system in early life.

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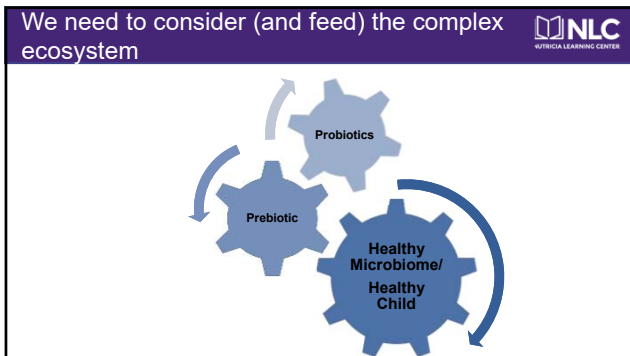
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