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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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Kelly Tappenden, Ph.D, R.D. Professor and Department Head Department of Kinesiology and Nutrition University of Illinois at Chicago



#### Learning Objectives

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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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Functions of the Intestinal Microbiota			
Functions	Mechanisms/Effects		
Digestive and metabolic functions	Vitamin production     Fermentation of nondigestible CHO → SCFA     Dietary carcinogens metabolism		
Neuronal development	<ul> <li>Modulation of brain gut axis during neuronal development</li> <li>Motor control and anxiety behavior</li> </ul>		
Protective functions against pathogenic bacteria	Pathogen displacement     Nutrient competition     Production of antimicrobial factors     Activation of local immune response     Contribute to the intestinal barrier function		
Immune development	IgA production     Control of local and general inflammation     Tightening of junctions     Induction of tolerance to foods		
	Buccharnesi et al. Curr Onin Gestmenterni 2013, 20:31–38		









with childhood diseases
Microbiota composition changes
Lack of bacteria of the phylum Bacteroidetes along with an abundance of Firmicutes
↓ concs of Faecalibacterium prausnitzii and Bifidobacteria ↑ levels of Escherichia coli Reduced diversity of gut microbiota
Significantly ↑ % of the class Gammaproteobacteria Presence of unusual Ruminococcus-like microbes
Predominance of Gammaproteobacteria ↓ diversity of gut microbiota
$\uparrow$ Firmicutes at expenses of the Bacteroidetes group
$\downarrow$ counts of lactic acid bacteria, clostridia, Bifidobacterium spp., Veillonella spp., and Bacteroides-Prevotella spp.
↓ counts of Lactobacilli, Bifidobacteria, and Bacteroides ↑ counts of Clostridium difficile ↓ diversity of gut microbiota







ergic phe	enotypes	velopment	
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	lgE, 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.





### Microbiota: human milk vs infant formula?

- Breast-fed infants
  - stable developing microbiota
  - dominated by bifidobacteria ('bifidofactor')
  - decreased pathogens
- Formula-fed infants



 assoc with higher incidence of pathogenic infections, diarrhea, pneumonia and allergy



rmsen et al., JPGN 2000:30;61-61







#### What is a PRObiotic?

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- 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)

#### What is a PREbiotic?

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- 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, 1985; 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 (Boekm 2002, 2003; Schmetze 2003; More 2003; Haarman & Knol 2005)
- Produced bacterial metabolites positively influence immune system (Boehm 2004; Vos 2007)

<ul> <li>Reduce the incidence of</li> </ul>	of allergy in the infants a	at risk (Arslanoglu 20	008; Van Hoffen 2009)	
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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?

## 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 longchain 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

## *Bifidobacterium breve* is safe in human infants

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- 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 (Fukishama Laboratory Fukushi Japan 1992), and in a dozen clinical trials









World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): <b>PREbiotics</b>	

**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-Garcia et al., World Allergy Organ

mal (2016) 9:1

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

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;
- using probiotics in women who breastfeed infants at high risk of developing allergy; and
- using probiotics in infants at high risk of developing allergy.

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

#### Conclusion

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Nutritional strategies employing PRObiotics AND PREbiotic fiber – hence SYNbiotics – are important for addressing dysbiosis of the developing intestinal microbiota and stimulating critical development of the immune system in early life.

