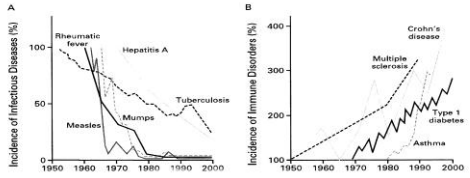
The Early Life Microbiome in the Emergence of Allergic Disease

Christina West MD, PhD
Department of Clinical Sciences, Pediatrics
Umeå University, Sweden

Immune disorders- a gut microbial deprivation disorder?

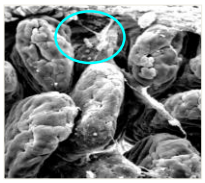


Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med. 2002;347:911-20.

Gut Microbiota

-a complex ecosystem based on mutual interaction with the host

- The total number of microbes in the gut, 10^{14} microorganisms, exceeds the number of human cells 10 times
- The corresponding collection of bacterial genes, microbiome, contains 100 times more genes than the human genome



Lactobacilli

Interplay between the microbiome and the immune system

Human microbiota dominated by 4 phyla

- Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria

(Dethlefsen et al. An ecological and evolutionary prespective on human-microbe mutualism and disease. Nature 2007; 449:811-18)

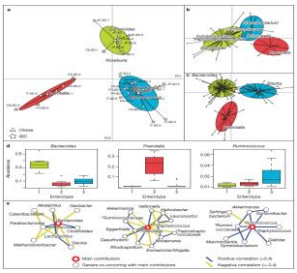
- The adult gut microbiota dominated by genera within Bacteroidetes and Firmicutes phyla
- A phylogenetic core gut microbiota has been suggested

(Tap J et al. Towards the human intestinal microbioa phylogenetic core. Environ Microbiol 2009; 11:2574-84)

- It has been estimated that the core gut microbiota contains ~1000 bacterial species

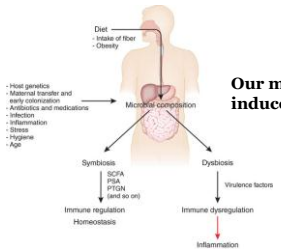
(Qin et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010; 464:59-65)

Microbiota variation stratified



- 3 distinct enterotypes in the intestinal microbiome in adults characterised by prominent genera
- Enterotype 1: *Bacteroides*
- Enterotype 2: *Prevotella*
- Enterotype 3: *Ruminococcus*
  - *Well-balanced host-microbial symbiotic states*
  - *Driven by species composition*
  - *Diet key modulator*
  - *Further functional analysis needed*

Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. Nature 2011; 473:174-180.



Our modern way of living induces a state of dysbiosis

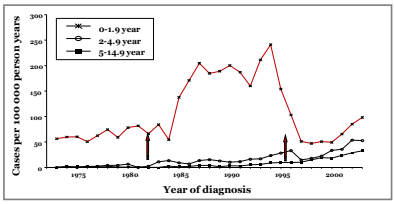
Maslowski KM, Mackay CR. Diet, gut microbiota and immune reponses. Nature Immunology 2011; 12(1):5-9.

Microbial imbalance and disease development

- *Dysbiosis* related to disease development
  - Allergic disease
  - Type 1 diabetes
  - Obesity
  - Atherosclerosis
  - IBD
  - Celiac disease

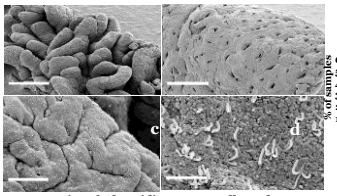
The Swedish Epidemic of Celiac disease

-Changed national guidelines on introduction of complementary foods

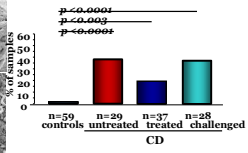


Ivarsson A, et al. Acta Paediatr. 2000;89:165-71
Olsson C, et al Pediatrics 2008;122:528-534

Other factors?
Rod-shaped bacteria adhere to the mucosa in CD patients



New species of Clostridium, Prevotella and Actinomyces graevenitzii



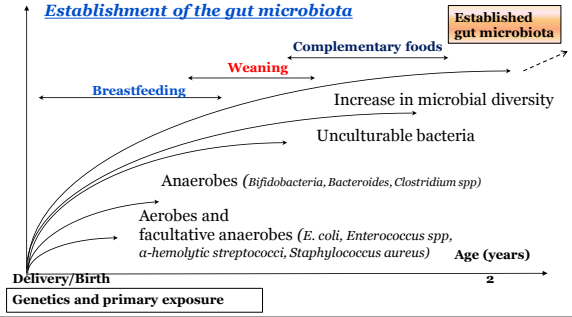
Forsberg G et al, Am J Gastroenterol. 2004;99:894-904.
Ou G et al, Am J Gastroenterol. 2009: 104:3058-67.

Gut colonization patterns

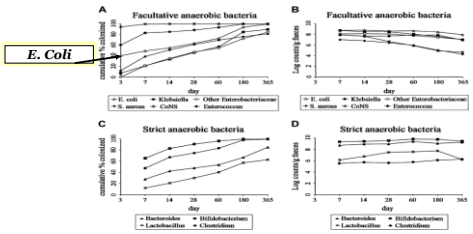
- Establishment of the early gut microbiota may impact upon infant and childhood development and immunity
- Gut colonization dependent on
  - genetics
  - delivery mode
  - maternal microbiota
  - environmental biota (hygiene level)
  - infant nutrition including the composition of breast milk

Adlerberth I, Wold AE. The establishment of the gut microbiota in Western infants. Acta Paediatr. 2009; 98:229-238.
Johnson CL, Versalovic J. The human microbiome and its potential importance to Pediatrics. Pediatrics 2012; 129:950-960.

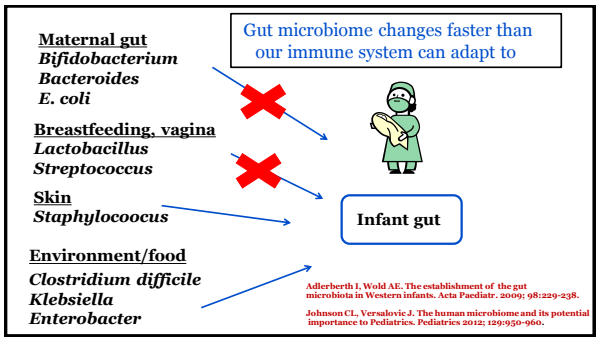
Establishment of the gut microbiota



A shift in gut colonization patterns



Adlerberth, Strachan DP, Matricardi PM, et al. Gut microbiota and development of atopic eczema in 3 European birth cohorts. JACI 2007; 120(2):343-50.



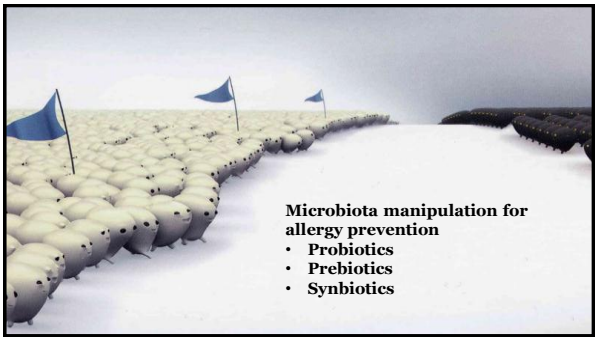
Gut microbiota and allergy development

- Differences in early gut microbiota precede the development of allergic disease
  (Björksten et al 2001, Kalliomäki et al 2001, Penders et al 2007, Sjögren et al 2009)
- Allergic infants less often colonised with *Bacteroides* and bifidobacteria
  (Björksten et al 2001, Sepp et al 2005, Hong et al 2010)
- Allergic infants more often colonized with *S. aureus*
  (Watanabe et al, 2003)
- Early colonisation with *C. difficile* associated with an increased risk of asthma
  (van Nimwegen et al, 2011)

Results variable across studies

Diversity and functional aspects

- Reduced microbial diversity associated with increased risk of developing eczema
  (Wang et al 2008, Abrahamsson et al 2012)
- Reduced microbial diversity associated with increased risk of developing rhinitis and IgE-sensitization
  (Bisgaard et al, 2012)
- Slow functional maturation of the gut microbiota associated with increased risk of developing allergic disease
  (Sandin et al 2009)



Hypothesis

Feeding Lactobacillus paracasei* ssp *paracasei* F19 (LF19) *during weaning would:

- **Maintain the presence of lactobacilli in the infant gut**
- **Adaptive immunity**
- **Allergy development**

Study design

Daily intake of cereals with (n=89) or without (n=90) LF19 10^8 CFU per serving daily

Infant age (mo) 4 — 13

Parents recorded in a diary intake of cereals, no of breastfeedings and any symptom of illness. Questionnaire monthly

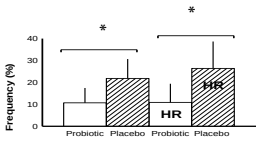
Immunizations at (3), 5½, 12 mo of age against diphteria, tetanus, pertussis, *Haemophilus influenzae* type b and polio

Venous blood was drawn before and 4 weeks after the second and third vaccine dose

Fecal samples were collected at 4 (entry), 6½, 9 and 13 mo

Reduced cumulative incidence of eczema by LF19

- In association with a higher IFN-γ/IL4 mRNA ratio
- No effects on IgE-sensitization



West CE et al, 2009

Prevalence of allergic sensitization and AD according to *Lactobacillus* species (KOALA cohort)

Lactobacillus	Present?	Sensitization % (cases/total)	AD* % (cases/total)
L. paracasei	No	28.4 (95/334)	18.1 (62/343)
	Yes	28.0 (44/157)	11.1 (18/162)
		P=0.92	***P*=0.04**
L. rhamnosus	No	27.3 (92/337)	15.3 (53/347)
	Yes	30.1 (46/153)	17.2 (27/157)
		P=0.53	*P*=0.58
L. acidophilus	No	28.0 (116/415)	17.1 (73/426)
	Yes	31.2 (24/77)	8.8 (7/80)
		P=0.57	*P*=0.06
Lactobacillus spp.	No	28.0 (94/336)	15.7 (54/345)
	Yes	29.5 (46/156)	16.1 (26/161)
		P=0.73	*P*=0.89

Penders J et al, 2010

The role of probiotics in allergy remains undecided

- Meta-analyses *suggest* a benefit of probiotics in reducing the development of eczema, including IgE-associated eczema, but not any other allergic outcomes
- The effect is moderate and the only probiotic strain with reproducible data is *Lactobacillus rhamnosus*
- Not enough evidence to recommend probiotics in the treatment or prevention of allergic disease

(West CE and Prescott SL, UptoDate 2012)

Pre- and probiotics for prevention of allergic disease and food hypersensitivity

Posters 1074 and 1075

John Sinn

The Cochrane Review

Clinical Use of Probiotics in Pediatric Allergy (CUPPA): A World Allergy Organization Position Paper

Alessandro Fiocchi, MD, chair,[1] Wesley Burks, MD, co-chair,[2] Sami L. Bahna, MD,[3] Leonard Bielory, MD,[4] Robert J. Boyle, MD,[5] Renata Cocco, MD,[6] Sten Dreborg, MD,[7] Richard Goodman, MD,[8] Mikael Kuitunen, MD,[9] Tari Haahtela, MD,[9] Ralf G. Heine, MD, FRACP,[10] Gideon Lack, MD,[11] David A. Osborn, MD,[12] Hugh Sampson, MD,[13] Gerald W. Tannock, PhD,[14] and Bee Wah Lee MD [15], on behalf of the WAO Special Committee on Food Allergy and Nutrition

- "...probiotic research is still in its infancy. There is need for basic microbiology research on the resident human microbiota. Mechanistic studies from biology, immunology and genetics are needed before we can claim to harness the potential of immune modulatory effects of the microbiota".
- "Probiotics do not have an established role in the prevention or treatment of allergy. No single probiotic supplement or class of supplements has been demonstrated to efficiently influence the course of any allergic manifestation".

WAO Journal 2012; 5:148–167

Summary and Perspectives

Current knowledge	Future challenges
The gut microbiome undergoes dynamic change during development and interacts with the developing immune system	✓The "healthy" infant gut microbiome promoting tolerance not yet characterised
Early gut microbial aberrancies have been associated with development allergic disease - no specific subset of the microbiota clearly associated with allergic disease	✓Further study of the role of total microbial diversity *vs.* diversity within specific genera ✓Studies assesing functional activity of the gut microbiome in relation to allergy development
Manipulation with prebiotics/probiotics/ synbiotics inconclusive in allergy prevention	✓Optimised prebiotics, probiotics and synbiotics ✓Clinical studies need to be combined with systems biology research

Collaborators

TORNADO

EU 7th Framework program

- Professor Olle Hernell, Dr Olof Sandström Department of Pediatrics, Umeå University
- Professor Marie-Louise Hammarström, Department of Microbiology, Immunology, Umeå University
- Associate professor Anneli Ivarsson, Department of Epidemiology, Umeå University
- Professors Marta Granström and Elisabeth Norin, Department of Microbiology, Tumor and Cell Biology (MTC), Clinical Microbiology, Karolinska Institute
- Professor Helena Käyhty, Department of Vaccines, KTL, Helsinki, Finland
- Dr Ulla Svensson, Dr Janet Håkansson, Arla Foods

Funding:

EU 7th Framework program, Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (FORMAS); Swedish Agency for Innovation Systems (VINNOVA); the Västerbotten county council (ALF); Swedish Nutrition and Allergy Foundations