ESTABLISHING THE MICROBIOME IN EARLY LIFE.

The role of prebiotics in infant nutrition and why it matters in infants with IEMs.

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DISCLOSURES

Dr. Kelly Tappenden received an honorarium provided by Nutricia for this presentation.

The above does not pose a conflict of interest for this presentation.

The opinions reflected in this presentation are those of the speaker and independent of Nutricia.

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OUTLINE

1. Understand the important of the intestinal microbiome;
2. Describe the role of prebiotics in infant nutrition;
3. Prebiotics in infants with inborn errors of metabolism

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A WORD UP FRONT…

This presentation will focus on **PRE-biotics**, not PRO-biotics.

- PRE-biotics are substrates that are selectively utilized by host microorganisms, conferring a health benefit *(Gibson, et al., 2017)*
- PRO-biotics are *live* microorganisms which when administered in adequate amounts confer a health benefit on the host *(Hill et al., 2014)*

Gibson, et al. (2017) Nat Rev Gastroenterol Hepatol. 14:491-502.
Hill, et al. (2014) Nat Rev Gastroenterol Hepatol. 11(8):506-14.

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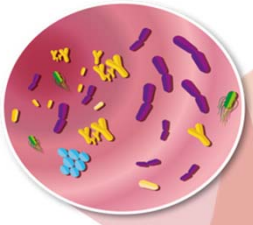
THE GUT MICROBIOME

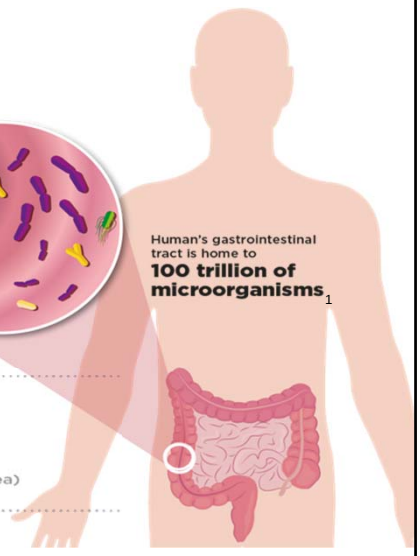
Gut microbiome and gut microbiota describe either the collective genomes of the microorganisms that resides in the gut, or the microorganisms themselves, respectively

The gut contains more than **3 million microbial genes**[1]
(150 times more than human genes)

Gut microbiota weighs up to **2 kg**[1]



Host-microbiome interactions can occur on a surface area of about
30–40m²
(20 times of the skin surface area)



1. Van de Wiele T et al. (2016) Nature Reviews Rheumatology. 12:398–411.

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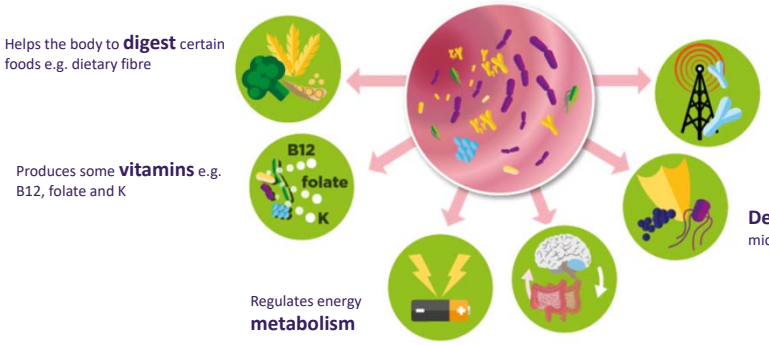
WHY IS GUT MICROBIOTA IMPORTANT?

A healthy gut microbiota contains a balanced composition of many classes of bacteria that have health-promoting functions



Shamir R et al. (2015) Essential Knowledge Briefing. Wiley, Chichester
Van de Wiele T et al.(2016) Nature Reviews Rheumatology. 12:398–411.

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FUNCTIONS OF THE INTESTINAL MICROBIOTA

Functions	Mechanisms/Effects
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
Digestive and metabolic functions	• Vitamin production • Fermentation of nondigestible CHO → SCFA • Dietary carcinogens metabolism
Neuronal development	• Modulation of brain gut axis during neuronal development • Motor control and anxiety behavior

Buccigrossi et al. (2013) Curr Opin Gastroenterol. 29:31–38

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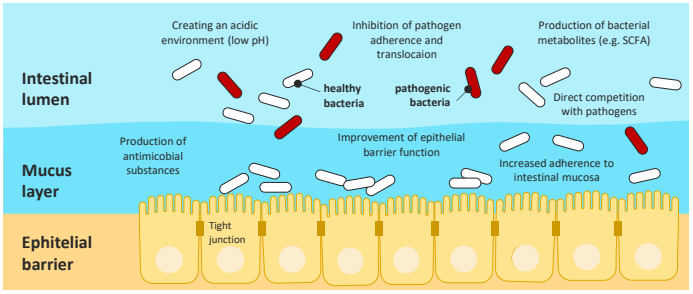
THE GUT MICROBIOTA ACTS AS A BARRIER AGAINST PATHOGENS

The healthy balanced gut microbiota acts a barrier against the infiltration and colonization and infiltration of pathogens, thereby protecting the infant against infections [1, 2]

EXAMPLES OF FACTORS IN A HEALTHY BALANCE GUT MICROBIOTA THAT PREVENT PATHOGEN GROWTH



1. Knol J. et al. (2005) Acta Pædiatrica. 94 (Suppl 449): 31–33.
2. Zhang M, et al. (2017) Front Immunol.8:942

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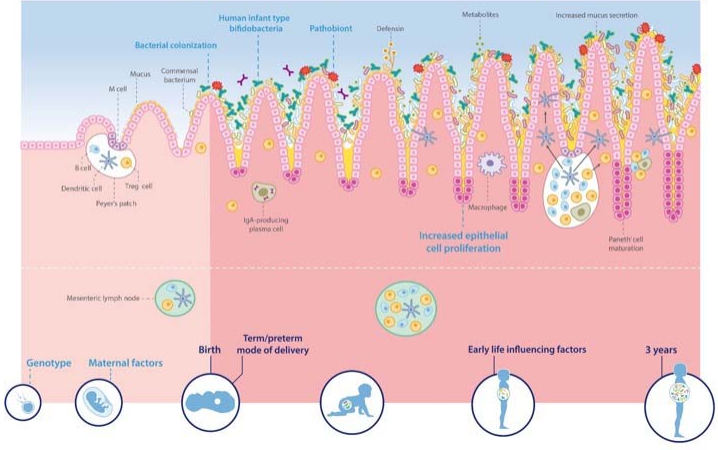
STIMULATE INTESTINAL IMMUNITY (GALT)

THE DEVELOPMENT OF IMMUNE SYSTEM THROUGH THE GUT

Normal gut, microbiota and immune development



70% of all immune cells are organized in the gut associated lymphoid tissue.

Immune maturation depends on gut microbiota signals.

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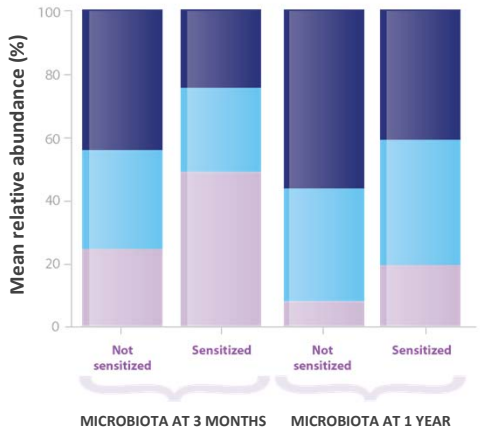
A HEALTHY GUT MICROBIOTA SUPPORTS ORAL TOLERANCE

DYSBIOSIS IN INFANT GUT MICROBIOTA PRECEDES FOOD SENSITIZATION



LOWER GUT MICROBIAL RICHNESS at age of 3 months is associated with INCREASED LIKELIHOOD OF FOOD SENSITIZATION by 1 year of age

Azad MB et al. (2015) Clinical & Experimental Allergy. 45: 632– 643

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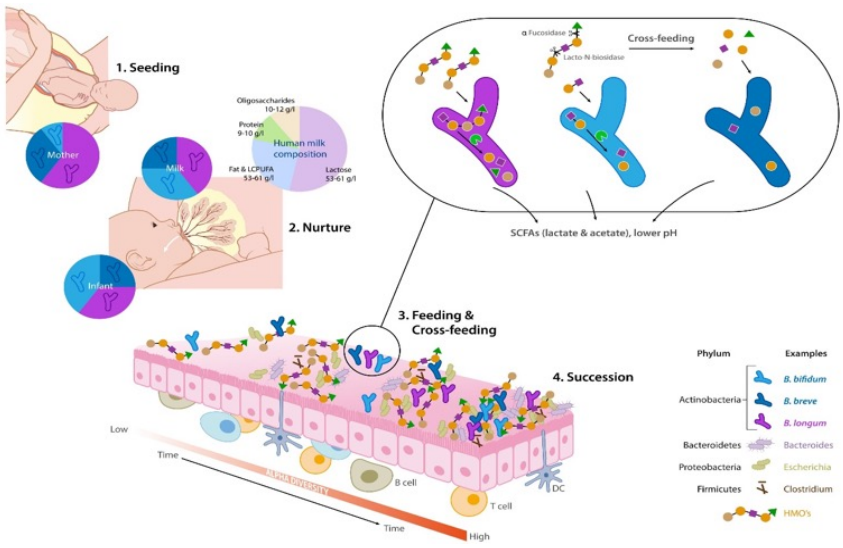
MICROBE CONTACT BEGINS *IN UTERO*



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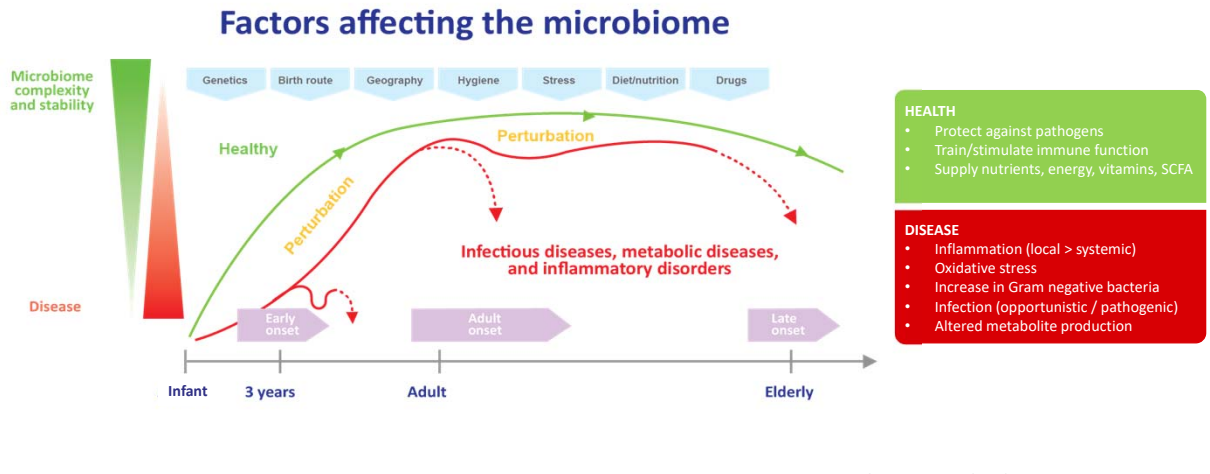
FACTORS AFFECTING STABILITY AND COMPLEXITY OF GUT MICROBIOME IN HEALTH AND DISEASE



Adapted from Kostic et al. (2014) Gastroenterology. 146:1489-1499

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FACTORS DISRUPTING MICROBIAL HOMEOSTASIS DURING EARLY LIFE AND DEVELOPMENT OR PROTECTION AGAINST DISEASES

Disruptive factor	Study	Cohort characteristics	Outcomes
C-section	Sevelsted et al.[25]	1.9 million Danish term children, ages 0-15 years	Asthma, systemic connective tissues disorders, juvenile arthritis, IBDs, immune deficiencies and leukemia
	Huh et al.[26]	1,255 US children, age 3 years	Obesity, higher body-mass index and sum of skinfolds
	Eggesbø et al.[27]	2,803 Norwegian children, 0-2 years	Reactions to egg, fish or nuts, and a fourfold increase in egg allergy
Antibiotic treatment	Risnes et al.[43] Hoskin-Parr et al.[44]	1,401 US children, ages 0-6 months 5,780 UK children, ages 0-2 years	Asthma and allergy Asthma and eczema
	Saari et al.[150]	12,062 Finnish children, ages 0-2 years	Overweight and obesity
	Schwartz et al.[151]	163,820 US children ages 2-18 years	Weight gain
	Kronman et al.[48]	9 million UK children	IBD development
Probiotics	Maldonado et al.[89]	215 Spanish children, ages 0-6 months	Reduction in gastrointestinal and upper respiratory tract infections
	Braegger et al.[76]	ESPGHAN Committee on Nutrition	Reduction in nonspecific gastrointestinal infections
Diet supplements	Zimmerman et al.[93]	Iron, 139 African children, ages 6-14 years	Intestinal inflammation, lower frequency of colic or irritability
Hygiene	Hesselmar et al.[96]	184 children, pacifier cleaning, ages 0-3 years	Lower risk of developing asthma, allergy and sensitization
Pets	Virtanen et al.[99]	3,143 Finnish children, ages 0-1 year	Reduction in risk of preclinical type I diabetes

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DYSBIOSIS IN INBORN ERRORS OF METABOLISM

The majority of studies on microbiome–IEM interactions have focused on PKU, with 1 study in HCU.

Study	Population	Microbiota composition changes
Pinheiro de Oliveira et al. (2016) - PKU	Compared the microbiome of 8 patients with PKU (ages 4.24 ± 1.74) to that of 10 healthy individuals	↓ levels of families *Clostridiaceae, Erysipelotrichaceae, and Lachnospiraceae, class Clostridiales, genera Coprococcus, Dorea, Lachnospira, Odoribacter, Ruminococcus,* and *Veillonella*. ↑ levels of *Prevotella, Akkermansia,* and *Peptostreptococcaceae* populations.
Elvira Verduci et al. (2018) - PKU	Compared gut microbiome of individuals ages 4-18: 21 with PKU on a low-Phe diet versus 21 with mild hyperphe on an unrestricted diet (same population for both studies	↓ overall microbial diversity & decreased fecal butyrate; specifically decrease in *Faecalibacterium spp.* & *Roseburia spp*.
Giulia Bassanini et al. (2019) - PKU		↓ *Faecalibacterium spp*. ↑ *Blautia spp.* and *Clostridium spp* (family *Lachnospiraceae*).
Gustavo Rizowy et al. (2020) - HCU	Compared fecal microbiota of 6 HCU patients (avg age 25) with age-matched healthy individuals	↑ levels of *Eubacterium coprostanoligenes* group and underrepresentation of the *Alistipes*, Family *XIII UCG-001*, and *Parabacteroidetes* genera Groups had similar gut microbiota diversity despite differences in the abundance of certain genera

Pinheiro de Oliveira, et al. (2016) PLoS ONE. 11(6): e0157513.
Verduci, et al (2018) Nutrition, Metabolism & Cardiovascular. 28, 385e392
Bassanini et al. (2019) Front Cell Infect Microbiol. 9:101.
Rizowy et al. (2020) Biochimie.173:3-11.

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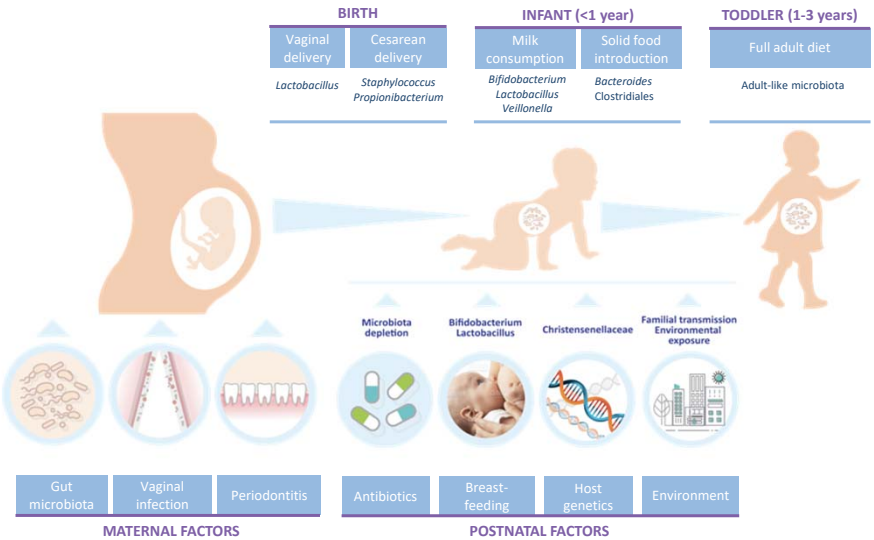
EARLY INTESTINAL MICROBIOTA DEVELOPMENT

A WINDOW OF OPPORTUNITY



Adapted from Tamburini et al. (2016). Nature Medicine. **22:** 713–722

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HUMAN MILK IS BEST FOR INFANT HEALTH

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HUMAN MILK IS BEST FOR INFANT HEALTH
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HUMAN MILK:
A COMPLEX SYSTEM WITH AN ORCHESTRA OF FUNCTIONS

88% Water +

	HMOs	Bacteria & Metabolites	Fat / LCPUFA	Lactose	Proteins	Hormones	Vitamins	Living Cells	Nucleo-tides	Minerals
Immunity	●	●	●	●	●		●	●	●	
Growth	●	●	●		●	●	●		●	●
Gut Health	●	●	●	●	●	●	●	●	●	●
Other	Microbiota	Microbiota Digestion	Brain Energy	Energy	Signaling	Mood			Brain	Bone & Teeth Blood

Pereira, PC (2014).Nutrition. 30(6): 619-627.

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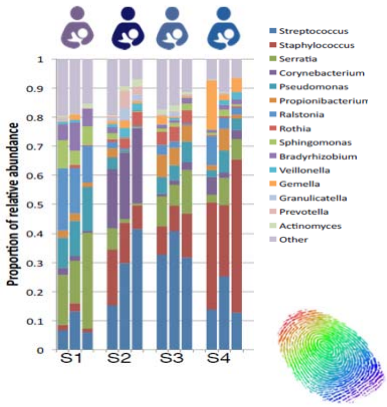
BACTERIA COMPOSITION OF HUMAN MILK IS HIGHLY VARIABLE

High inter-individual variability (1)



HM contains 10^3-10^5 Colony Forming Units/ml bacteria, including Lactobacilli, Bifidobacterium and Staphylococcus (1 - 3).

Lactic acid bacteria in human milk ≠ Vagina or skin of the mother (2)

1. *Hunt et al. (2011). Plos ONE: 21313*
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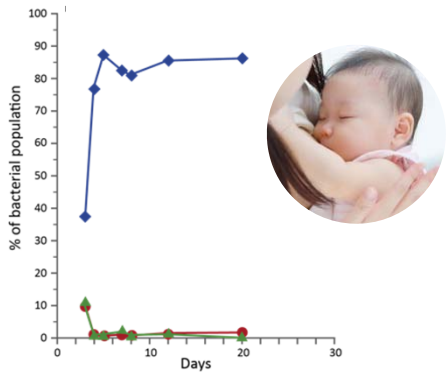
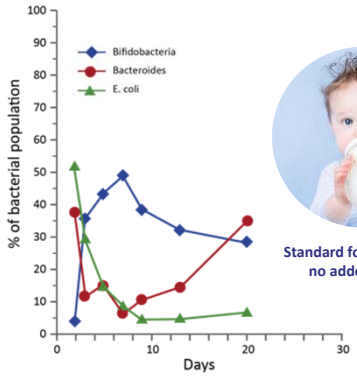
MICROBIOTA: BREAST VS BOTTLE?

HIGHER BIFIDOBACTERIA COUNT IN BABIES WHO BREASTFEED

Breastfeeding



Formula Feeding



Standard formula milk with no added prebiotics

Harmsen HJ, et al. (2000) J Pediatr Gastroenterol Nutr. 30:61-67.

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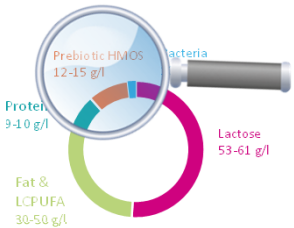
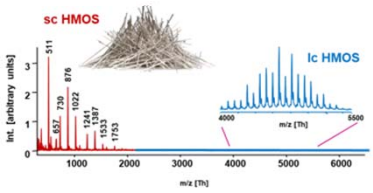
PREBIOTIC HMOs: A KEY COMPONENT OF HUMAN MILK

PREBIOTIC HMOs CONSIST OF DIFFERENT STRUCTURES WITH >162 IDENTIFIED





1000s of structures

Stahl B et al. (1994) Analyt Biochem. 223:218-226

162 structures identified

Urashima T et al. (2018) Trends Glycosci. Glycotechnol . 30 (172): 51-65

Key Milestones:

- Egge 1991 FABMS of HMOS
- Stahl 1991 MALDI-Mass Spec of OS
- Thurl 1991 LC of sc HMOS
- Stahl 1994 Mass Spec of sc & lc HMOS
- Thurl 1996 4 types of HMOS based on genes
- Thurl 2017 Systematic Rev on HMOS quantities
- Mank 2019 New LC Mass Spec of Key HMOS

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PREBIOTIC HMOs: A KEY COMPONENT OF HUMAN MILK

HMOs HAVE A MULTITUDE OF FUNCTIONS

Prebiotic Effect: Growth and Activity of Beneficial Bacteria

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Brain Building Blocks

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Direct Effect on Immune Cells

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Anti-Infective Effect as Receptor Analogues

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CAN NUTRITIONAL FORMULAS BE MODIFIED TO ALTER THE INTESTINAL MICROBIOTA AND IMPROVE CLINICAL OUTCOMES IN CHILDREN?

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PREBIOTICS IN HM AND INFANT FORMULA WITH scGOS/lcFOS

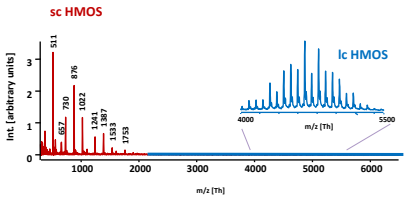
HUMAN MILK OLIGOSACCHARIDES

1000s of structures

Stahl B, Thurl S, et al. (1994) Analyt. Biochem.; 223:218-226

162 structures identified

Urashima T, Hirabayashi J, Sato A, Kobata A Trends Glycosci. Glycotechnol. (2018), 30; 172, 51-65

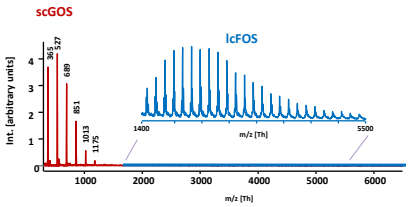


INFANT NUTRITION WITH scGOS/lcFOS (9:1)

100s of structures

Coulier L et al. (2009) J. Agric. Food Chem.; 57, 8488–8495

Finke et al. (2002) J. Agric. Food Chem,; 50, 4743-4748



Boehm G, et al. (2003) Acta Paediatr Suppl. 91(441):64-7

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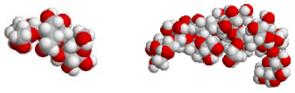
PREBIOTICS AND BIFIDOGENIC GUT COLONIZATION

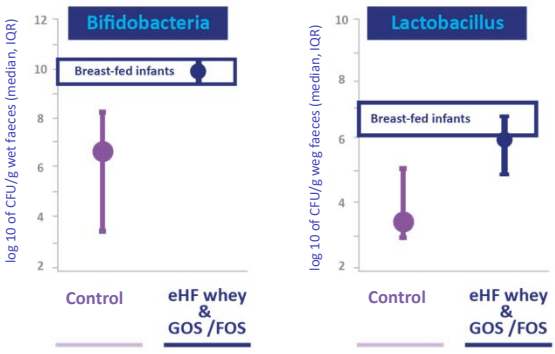
scGOS & lcFOS



- 6 clinical trials
- With a specific mixture of short-chain galacto-oligosaccharides (scGOS) and long chain fructo-oligosaccharides (lcFOS)
- In a ratio 9:1 in infant milk formulas
- Showed consistent positive effects on stool consistency and stool frequency

Reviewed in Scholtens et al. (2014) World Gastroenterol

EFFECT ON GUT MICROFLORA (TERM INFANTS AFTER 28 DAYS FORMULA FEEDING)



Moro et al. (2002) J Ped Gastroenterology & Nutrition. 34 (3): 291-295

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scGOS/lcFOS SUPPORTS MICROBIOTA BY DISCOURAGING THE GROWTH OF POTENTIAL PATHOGENS

Target population Preterm

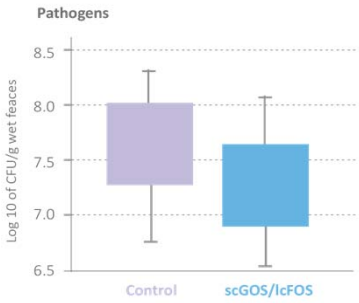
Conclusions

Supplementation of a preterm formula with scGOS/lcFOS sign decreases the sum of pathogens. Also the sum of pathogens as % of total bacterial count was lower than control.

Study design

25 preterm infants

- 0.0g scGOS/lcFOS [Control] (n=15)
- 1.0 g/100ml scGOS/lcFOS (n=12)



scGOS/lcFOS sign reduces the number of clinically relevant pathogens in stools of preterm infants

Knol J. et al. (2005) Acta Pædiatrica. 94 (Suppl 449): 31–33.

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scGOS/lcFOS REDUCES INFECTIONS DURING THE FIRST 6 MONTHS OF LIFE

Target population Healthy infants

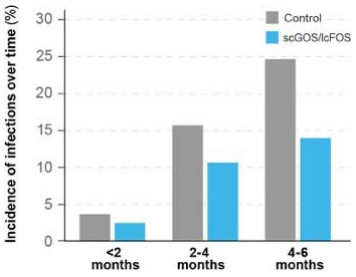
Conclusions

0.8 g/ 100ml scGOS/lcFOS reduced the number of infectious episodes during the first 6 months of life.

Study design

Randomized, double blind, controlled study; Healthy, term infants with parental history of atopic eczema, allergic rhinitis, or asthma:

- 0.0 g scGOS/lcFOS [Control] (n=104)
- 0.8 g/100ml scGOS/lcFOS (n=102)



scGOS/lcFOS results in lower incidence of infections over time

Arslanoglu et al. (2007). Journal of Nutrition *137:2420-2424*

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scGOS/lcFOS REDUCES INFECTIONS AND INCIDENCE OF ALLERGIC MANIFESTATIONS DURING THE FIRST 2 YRS OF LIFE

Target population Healthy infants

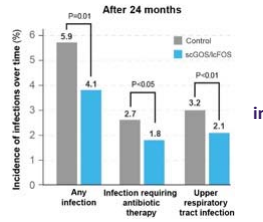
Conclusions

Early nutritional intervention with 0.8 g/100ml scGOS/lcFOS is effective in priming the infant's immune system, providing substantial protection against both allergy and infection.

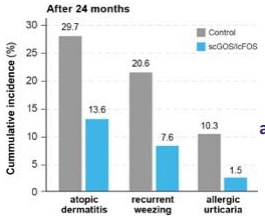
Study design

Randomized, double blind, controlled study; Healthy, term infants with parental history of atopic eczema, allergic rhinitis, or asthma; for 2 years:

- 0.0 g scGOS/lcFOS [Control] (n=68)
- 0.8 g/100ml scGOS/lcFOS (n=66)



scGOS/lcFOS results in sign. lower number of overall infections, URTI and infections requiring antibiotics



scGOS/lcFOS results in sign. lower cumulative incidence of atopic dermatitis, wheezing and allergic urticaria

Arslanoglu et al.(2008) Journal of Nutrition.138:1091-1095

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scGOS/lcFOS REDUCES INTESTINAL INFECTIONS

Target population Healthy infants

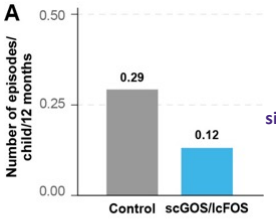
Conclusions

These data show that scGOS/lcFOS 0.4 g/100 ml reduced intestinal infections in healthy infants during the first year of age.

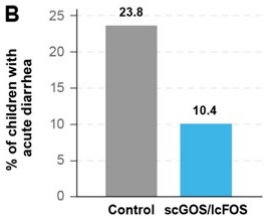
Study design

A prospective, randomized, controlled, open trial.
Healthy infants aged between 15 and 120 days were enrolled in two intervention groups; formula feeding for 12 months

- 0.0 g scGOS/lcFOS [Control] (n=105)
- 0.4 g/ 100mL scGOS/lcFOS (n=96)



scGOS/lcFOS leads to significant lower number of gastroenteritis episodes



scGOS/lcFOS results in 58% less acute diarrhea

Bruzzese et al. (2009) Clinical Nutrition. 28:156-161

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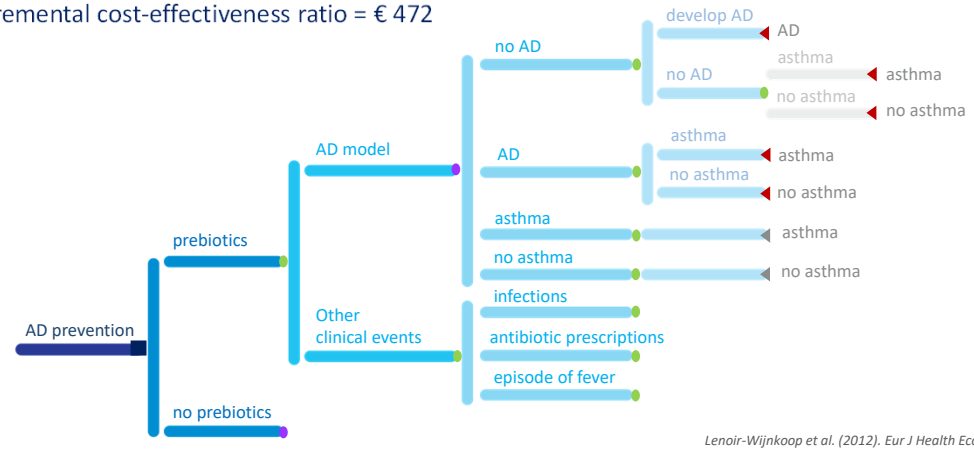
USE OF FORMULA WITH scGOS/lcFOS PREBIOTICS RESULT IN POSITIVE SHORT- AND LONG-TERM HEALTH ECONOMIC BENEFITS

- Prebiotic cost = €51
- Quality Adjusted Life Years = 0.108
- Incremental cost-effectiveness ratio = € 472



Lenoir-Wijnkoop et al. (2012). Eur J Health Econ. 13:101–110.

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PREBIOTICS FOR INFANTS WITH IEM

There is no indication that infants with IEM should be any different from healthy infants when it comes to prebiotics (with the potential exception of MMA/PA patients).

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DYSBIOSIS IN INBORN ERRORS OF METABOLISM

The majority of studies on microbiome–IEM interactions have focused on PKU, with 1 study in HCU.

Study	Population	Microbiota composition changes
Pinheiro de Oliveira et al. (2016) - PKU	Compared the microbiome of 8 patients with PKU (ages 4.24 ± 1.74) to that of 10 healthy individuals	↓ levels of families *Clostridiaceae, Erysipelotrichaceae, and Lachnospiraceae, class Clostridiales, genera Coprococcus, Dorea, Lachnospira, Odoribacter, Ruminococcus,* and *Veillonella*. ↑ levels of *Prevotella, Akkermansia,* and *Peptostreptococcaceae* populations.
Elvira Verduci et al. (2018) - PKU	Compared gut microbiome of individuals ages 4-18: 21 with PKU on a low-Phe diet versus 21 with mild hyperphe on an unrestricted diet (same population for both studies	↓ overall microbial diversity & decreased fecal butyrate; specifically decrease in *Faecalibacterium spp.* & *Roseburia spp*.
Giulia Bassanini et al. (2019) - PKU		↓ *Faecalibacterium spp*. ↑ *Blautia spp.* and *Clostridium spp* (family *Lachnospiraceae*).
Gustavo Rizowy et al. (2020) - HCU	Compared fecal microbiota of 6 HCU patients (avg age 25) with age-matched healthy individuals	↑ levels of *Eubacterium coprostanoligenes* group and underrepresentation of the *Alistipes*, Family *XIII UCG-001*, and *Parabacteroidetes* genera Groups had similar gut microbiota diversity despite differences in the abundance of certain genera

Pinheiro de Oliveira et al. (2016) PLoS ONE 11(6): e0157513.
Verduci et al (2018) Nutrition, Metabolism & Cardiovascular. 28, 385e392
Bassanini et al. (2019) Front Cell Infect Microbiol. Apr 16;9:101.
Rizowy et al. (2020) Biochimie.173:3-11.

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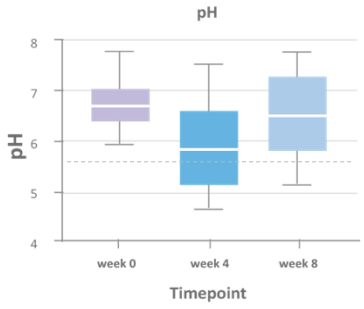
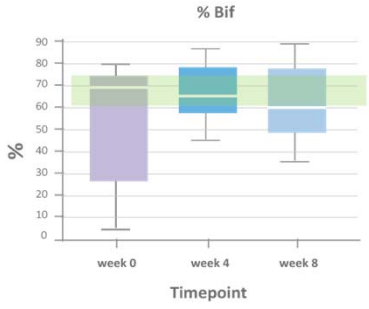
scGOS/lcFOS IN AMINO ACID FORMULA SUPPORTS MICROBIOME IN INFANTS WITH PHENYLKETONURIA

Use of PKU infant formula with scGOS/lcFOS in pilot study with 9 infants:
8-week, open label intervention

- **Well tolerated**
- **Lowered pH**
- **Maintained levels of bifidobacteria**





Typical concentrations found in healthy breast-fed infants

MacDonald et al. (2011) Mol Gen Metab.104:555–559

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USAGE OF PREBIOTICS: POTENTIAL CONCERN FOR MMA/PA PATIENTS?

Propionate production in MMA/PA patients

- 52% amino acid catabolism
- **~ 25% attributed to gut bacteria**
- ± 30% unaccounted

Thompson et al. (1990) Metabolism. 39(11):1133-1137

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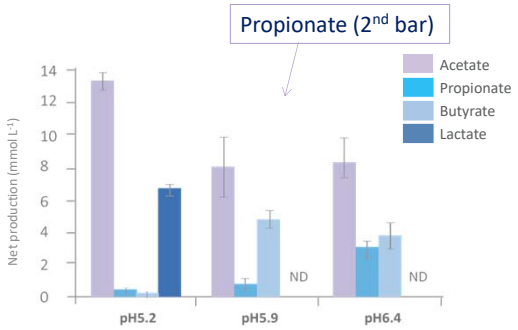
LOWER GUT pH RESULTS IN LOWER PROPIONATE PRODUCTION

- **Study: Fecal inocula from healthy adult volunteers**
- **Gut pH has influence on short-chain fatty acid production (incl. propionate)**

Gut pH	Propionate production
pH 6.4	Occurred
pH 5.9	Inhibited
pH 5.2	Curtailed



Effect of initial pH on net production of the major SCFA from 24-h batch culture incubations with a mixture of carbohydrates. Error bars indicate standard errors of the means, ND, not detected.

Belenguer A et al. (2007) Applied and Environmental Microbiology. 6526-6533

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RESEARCH SHOWS scGOS/lcFOS MAY HELP REDUCE PROPIONATE PRODUCTION IN THE GUT.

PREBIOTICS MAY HAVE A BENEFICIAL EFFECT

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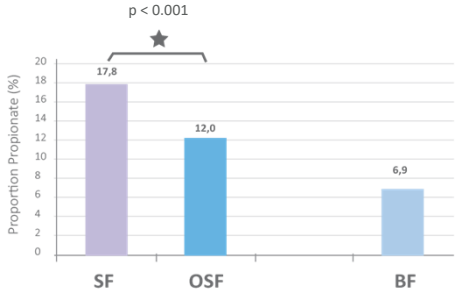
REDUCED PROPIONATE PRODUCTION IN HEALTHY INFANTS FED scGOS/lcFOS INFANT FORMULA

- Randomized DBPC with 53 infants, fully formula-fed, were given either formula with or without scGOS/lcFOS

Results:

- Higher bifidobacteria proportion → influence on SCFA production
- Lower pH
- Increased acetate and lower propionate



Knol et al. (2005) JPGN. 4:36-42

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REDUCED PROPIONATE PRODUCTION IN HEALTHY INFANTS FED scGOS/lcFOS INFANT FORMULA

- **Randomized DB study with infants fed 3 different types of formulas**

- **"Infants fed the scGOS/lcFOS formula had higher percentages of acetate and lower percentages of propionate, butyrate ..compared with infants fed the standard … formula."**

Bakker-Zierikzee et al. (2005) British Journal of Nutrition. 94:783–790

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RECENT EXPERT OPINION ON GUT MICROBIOTA IN MMA/PA

Dietary management of MMA/PA may be improved by specific prebiotics that modify gut microbiota to stabilize or possibly reduce PA production

- Gut microbiota is a potentially modifiable target for propionate production.
- Propiogenic prebiotics should be avoided to stabilize PA production.
- **Specific prebiotics may reduce propionate production in the gut.**

Burlina et al. (2018) . Expert Opinion on Orphan Drugs. 6:(11) 683-692

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TAKE HOME MESSAGES

- Prebiotic fiber is fermented by the commensal microbiota and hence stimulates the important biological functions of the microbiota previously outlined and corrects the dysbiosis associated with various diagnoses.
- Infants with inborn errors of metabolism may benefit from the addition of scGOS/lcFOS to (metabolic) infant formulas, especially as we learn more about dysbiosis in this patient population.
- **There does not seem an additional risk for gut propionate production when providing GOS/FOS to MMA/PA patients.**

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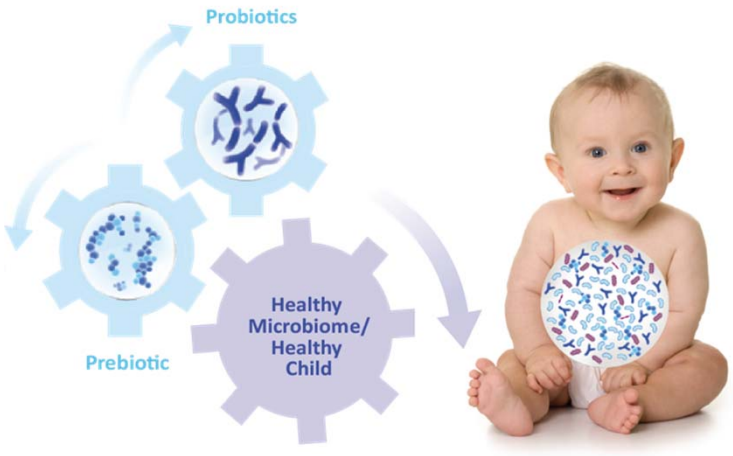
WE NEED TO CONSIDER (AND FEED) THE COMPLEX ECOSYSTEM



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THANK YOU!

QUESTIONS?

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PLEASE PROVIDE US WITH YOUR FEEDBACK

YOU CAN EITHER SCAN THE QR CODE OR
FILL OUT THE SURVEY AS YOU EXIT THE WEBINAR

FOR US PARTICIPANTS ONLY:
PLEASE LOOK OUT FOR A SEPARATE EMAIL FROM NUTRICIA REGARDING CE CREDITS

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