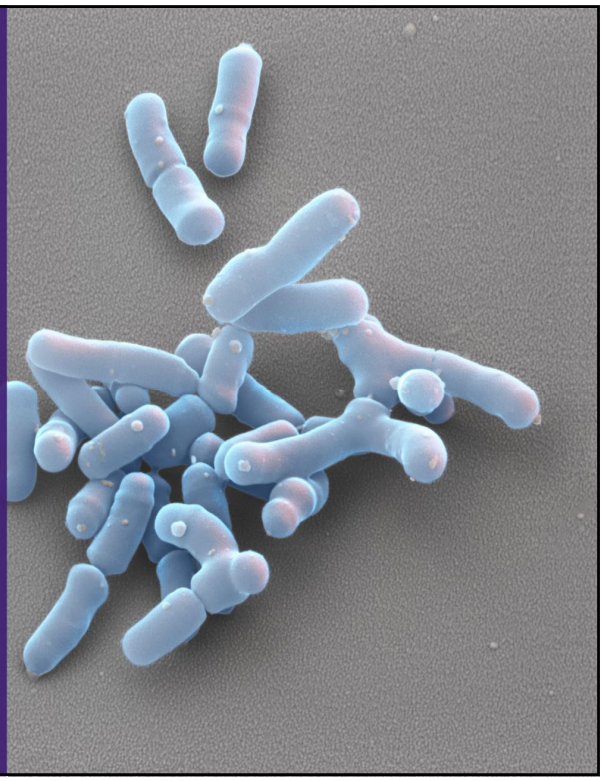
NLC
NUTRICIA LEARNING CENTER

Practical Management of Infants with Cow Milk Allergy and the Role of the Intestinal Microbiota. Are We Doing Enough?



Kelly Tappenden, PhD, RD, FASPEN
Professor and Head,
Dept of Kinesiology and Nutrition
University Teacher Scholar
University of Illinois - Chicago

1

Disclosures

NLC
NUTRICIA LEARNING CENTER

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.

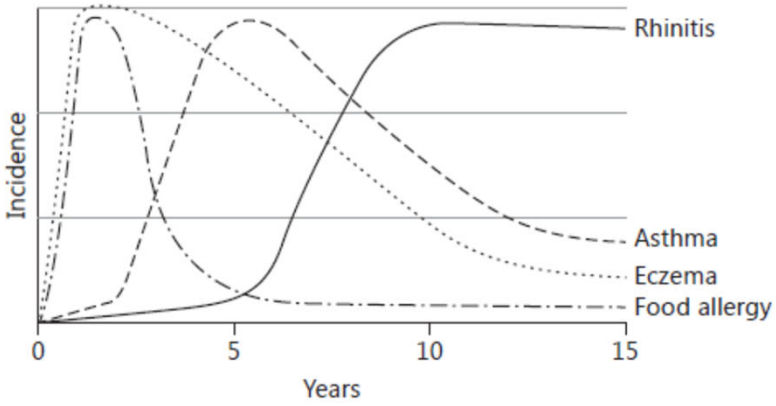
2

Learning Objectives

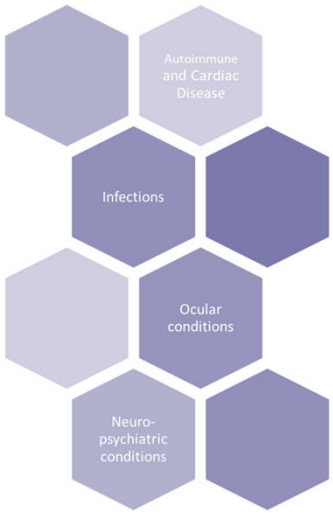
- Demonstrate the importance of the intestinal microbiota in early life and the development of the immune system;
- Explore data on the immune system and infections in those with cow milk allergy;
- Illustrate the role of specific prebiotics and probiotics in the dietary management of infants with cow milk allergy;
- Discover tips for clinicians based on a growing body of evidence.

3

Atopy comorbidities vary by age through adulthood



Nutten. Ann Nutr Metab 2015;66(suppl1):8-16.



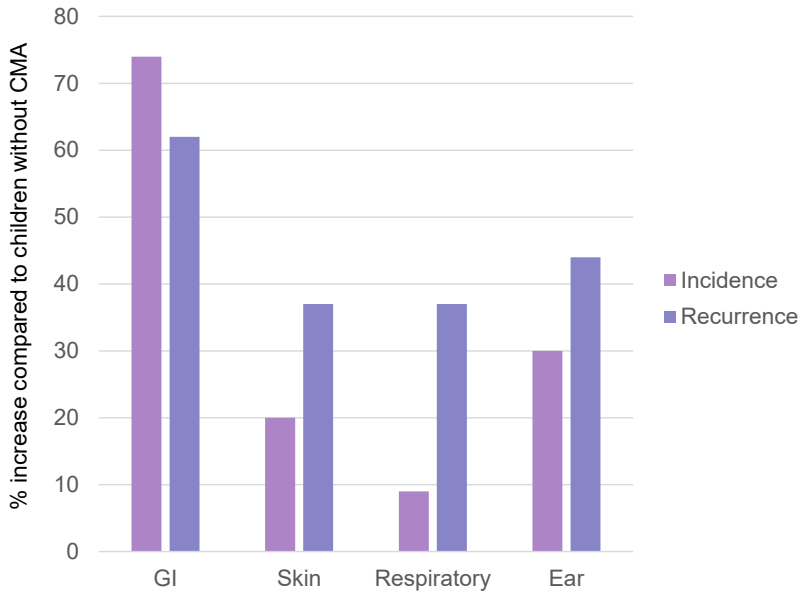
https://nationaleczema.org/research/eczema-facts/

4

Cow milk allergy (CMA) is a significant burden in early childhood

NLC NUTRICIA LEARNING CENTER

MORE CHILDREN WITH CMA HAD SYMPTOMS AFFECTING MULTIPLE SYSTEMS.



Fiocchi et al., 2021. Nutrients.

Sorensen et al., 2022. Immunity, Inflammation and Disease.

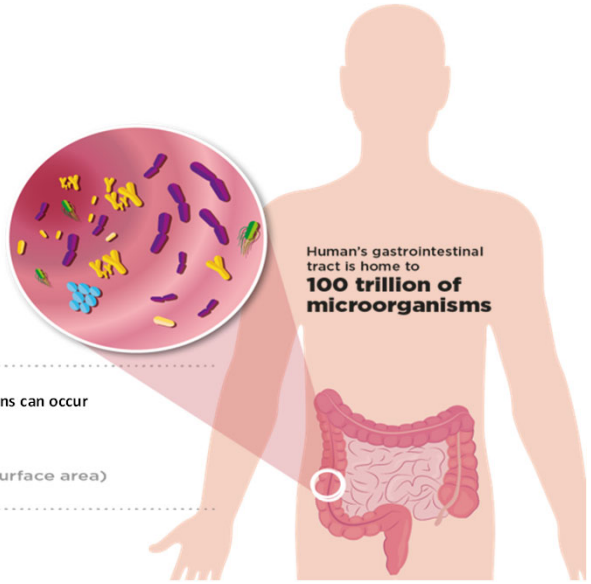
5

The Intestinal Microbiota

NLC NUTRICIA LEARNING CENTER

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 hosts 70-80% of the human body's immune cells



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

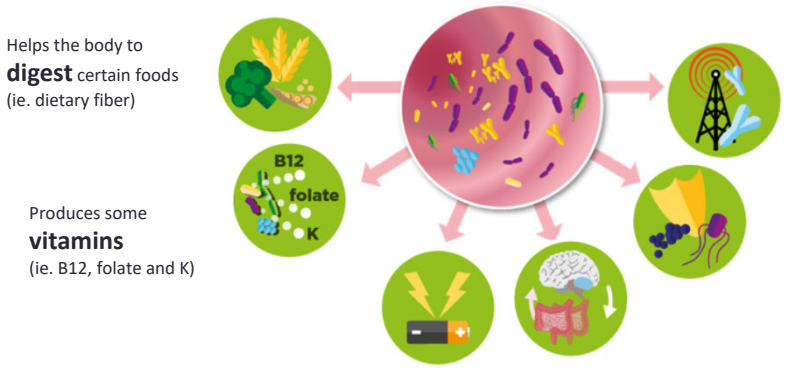
Host-microbiome interactions can occur on a surface area of about **30–40m²** (20 times of the skin surface area)

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

Van de Wiele T et al. *Nature Reviews Rheumatology*, 12:398–411, 2016.

6

Why is intestinal microbiota important?



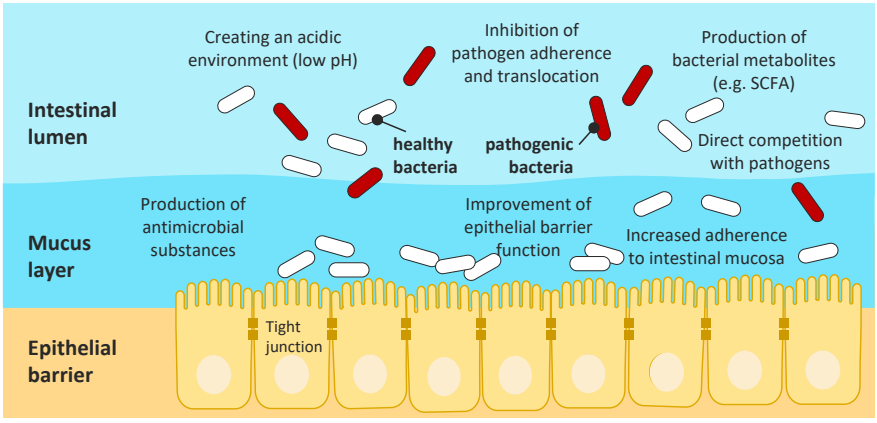
Shamir R, et al. *Essential Knowlede Briefing*, Wiley, Chichester (2015).
Van de Wiele T et al. *Nature Reviews Rheumatology*, 12:398–411, 2016.

7

The gut microbiota acts as a barrier against pathogens

The healthy balanced intestinal microbiota acts a barrier against the infiltration and colonization and infiltration of pathogens, thereby protecting the infant against infections.

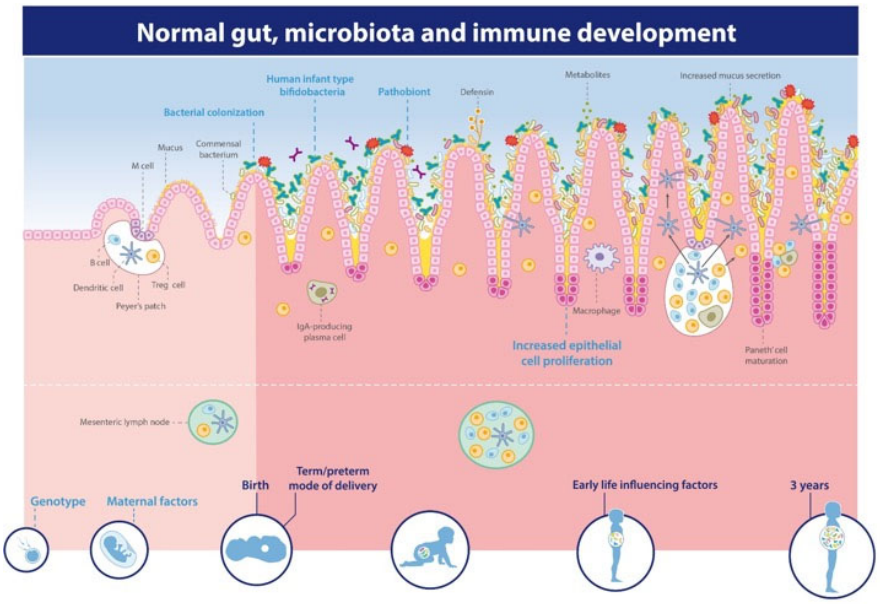
EXAMPLES OF FACTORS IN A HEALTHY BALANCED INTESTINAL MICROBIOTA THAT PREVENT PATHOGEN GROWTH



Zhang M, et al. *Front Immunol.* 2017;8:942

8

Development of the immune system starts with the intestinal microbiota



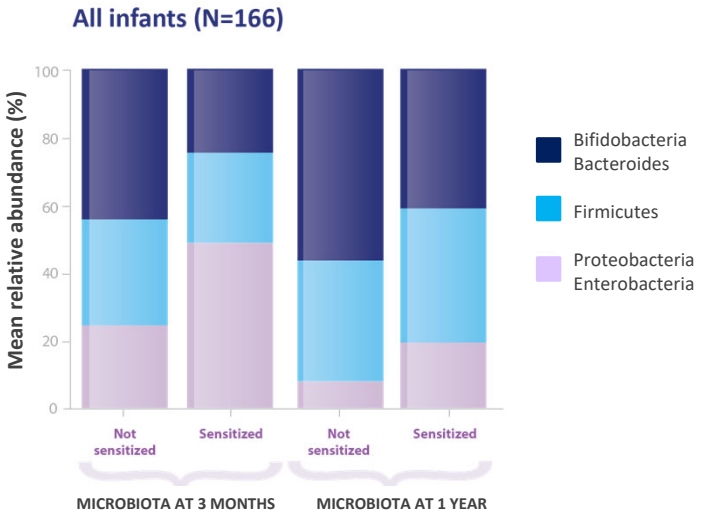
70-80% of all immune cells are organized in the gut associated lymphoid tissue.

Immune maturation depends on gut microbiota signals.

9

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 et al., 2015. Clinical and Experimental Allergy

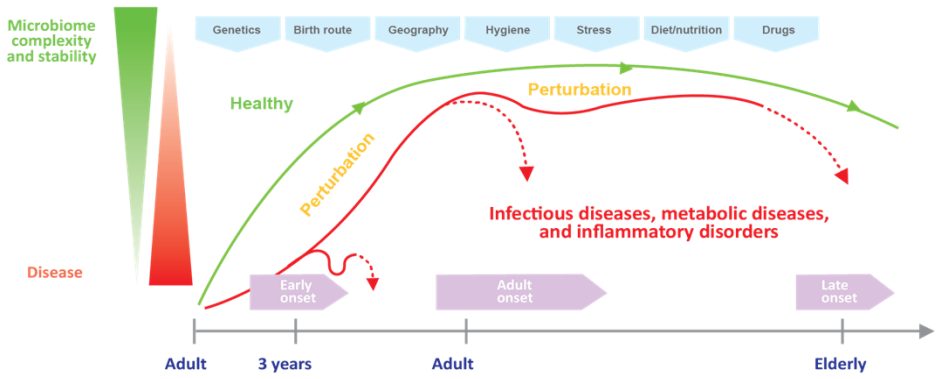
10

Dysbiosis precedes development of allergic phenotype

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.

11

Factors affecting stability and complexity of gut microbiome in health and disease



HEALTH
- Protect against pathogens
- Train/stimulate immune function
- Supply nutrients, energy, vitamins, SCFA

DISEASE
- Inflammation (local > systemic)
- Oxidative stress
- Increase in Gram negative bacteria
- Infection (opportunistic / pathogenic)
- Altered metabolite production

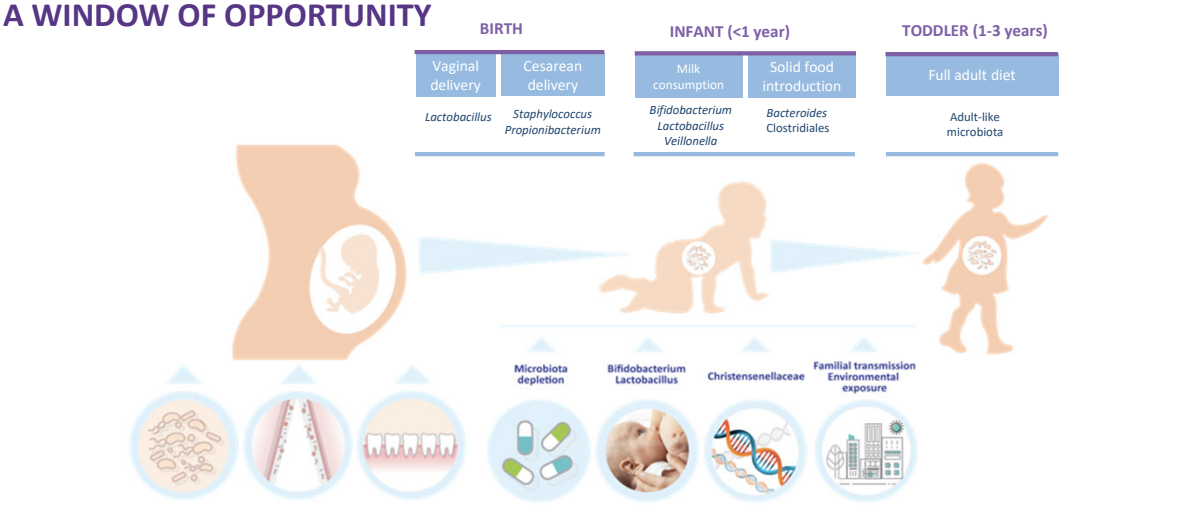
Adapted from Kostic et al., Gastroenterology 2014;146:1489-1499.

12

Early intestinal microbiota development

NLC NUTRICIA LEARNING CENTER

A WINDOW OF OPPORTUNITY



Adapted from Tamburini et al., *Nature Medicine*, 2016;22(7):713-722.

13

Factors disrupting microbial homeostasis during early life and development or protection against diseases

NLC NUTRICIA LEARNING CENTER

Disruptive factor	Study	Cohort characteristics	Outcomes
C-section	Sevelsted et al., 2015	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., 2012	1,255 US children, age 3 years	Obesity, higher body-mass index and sum of skinfolds
	Eggesbø et al., 2003	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., 2011 Hoskin-Parr et al., 2013	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., 2015	12,062 Finnish children, ages 0-2 years	Overweight and obesity
	Schwartz et al. 2016	163,820 US children ages 2-18 years	Weight gain
	Kronman et al., 2012	9 million UK children	IBD development
Probiotics	Maldonado et al., 2012	215 Spanish children, ages 0-6 months	Reduction in gastrointestinal and upper respiratory tract infections
	Braegger et al., 2011	ESPGHAN Committee on Nutrition	Reduction in nonspecific gastrointestinal infections
Diet supplements	Zimmerman et al., 2010	Iron, 139 African children, ages 6-14 years	Intestinal inflammation, lower frequency of colic or irritability
Hygiene	Hesselmar et al., 2013	184 children, pacifier cleaning, ages 0-3 years	Lower risk of developing asthma, allergy and sensitization
Pets	Virtanen et al., 2014	3,143 Finnish children, ages 0-1 year	Reduction in risk of preclinical type I diabetes

Adapted from Tamburini et al., *Nature Medicine*, 2016;22(7):713-722.

14

HUMAN milk is best for infant health

NLC NUTRICIA LEARNING CENTER

- Optimal growth & maturation[1-6]
- Brain & eye development[7-9]
- Infections and illnesses[10-15]
- Sudden Infant Death Syndrome (SIDS)[16-21]
- Cognitive development[22-24]
- Allergies and asthma[16, 25-31]
- Pediatric cancers[16, 32]
- Childhood obesity[33-44]
- Cardiovascular and metabolic diseases[16, 36, 45]
- Diarrhea[43, 46-49]

15

HUMAN milk is best for infant health References

NLC NUTRICIA LEARNING CENTER

1. Dietitians of Canada, Canadian Paediatric Society, College of Family Physicians of Canada, Community Health Nurses of Canada, Secker D. Promoting optimal monitoring of child growth in Canada: using the new WHO growth charts. Can J Diet Pract Res 2010; 71: e1-3.
2. Villar J, Papageorghiou AT, Pang R, et al. Monitoring human growth and development: a continuum from the womb to the classroom. Am J Obstet Gynecol 2015; 213: 494-9.
3. World Health Organization Multicenter Growth Reference Study Group. WHO Child Growth Standards: Methods and Development. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index for age: methods and development. 2006. Available at: http://www.who.int/childgrowth/standards/technical_report/en/index.html. Accessed 19 October, 2015.
4. Turck D, Michaelsen KF, Shamir R, et al. World Health Organization 2006 child growth standards and 2007 growth reference charts: A discussion paper by the committee on Nutrition of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2013; 57: 258-64.
5. World Health Organization. Nutrition. Exclusive breastfeeding. Available at: http://www.who.int/nutrition/topics/exclusive_breastfeeding/en/. Accessed 10 December, 2015.
6. World Health Organization. The optimal duration of exclusive breastfeeding: report of an expert consultation. Available at: http://www.who.int/nutrition/topics/optimal_duration_of_exc_bfeeding_review_eng.pdf. Accessed 23 December, 2015.
7. Martin, R., Nauta, A., Ben Amor, K., Knippels, L., Knol, J., & Garssen, J. (2010). Early life: gut microbiota and immune development in infancy.Beneficial microbes, 1(4), 367-382.
8. Jeurink, P. V., Van Bergenhenegouwen, J., Jimenez, E., Knippels, L. M. J., Fernandez, L., Garssen, J., ... & Martin, R. (2012). Human milk: a source of more life than we imagine. Beneficial microbes, 4(1), 17-30.
9. Nauta, A. J., & Garssen, J. (2013). Evidence-based benefits of specific mixtures of non-digestible oligosaccharides on the immune system.Carbohydrate polymers, 93(1), 263-265.
10. Kramer, M. S., Chalmers, B., Hodnett, E. D., Sevkovskaya, Z., Dzikovich, I., Shapiro, S., Collet, J. P., Vanilovich, I., Mezen, I., Ducruet, T., & Shishko, G. (2001). Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. Journal of the American Medical Association, 285(4), 413-420.
11. Kramer, M. S., Guo, T., Platt, R. W., Sevkovskaya, Z., Dzikovich, I., Collet, J. P., Shapiro, S., Chalmers, B., Hodnett, E., Vanilovich, I., & Mezen, I. (2003). Infant growth and health outcomes associated with 3 compared with 6 mo of exclusive breastfeeding. The American Journal of Clinical Nutrition, 78(2), 291-295.
12. Chien, P. F., & Howie, P. W. (2001). Breast milk and the risk of opportunistic infection in infancy in industrialized and non-industrialized settings. In: Advances in Nutritional Research (pp. 69-104). Springer US.
13. Duijts, L., Jaddoe, V. W., Hofman, A., & Moll, H. A. (2010). Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. Pediatrics, 126(1), e18-e25.
14. Bachrach, V. R. G., Schwarz, E., & Bachrach, L. R. (2003). Breastfeeding and the risk of hospitalization for respiratory disease in infancy: a meta-analysis. Archives of pediatrics & adolescent medicine, 157(3), 237-243.
15. Riordan, J., & Wambach, K. (2010). Chapter 4: The biological specificity of breast milk. In: Breastfeeding and Human breastfeeding. Jones & Bartlett Learning.
16. Ip, S., Chung, M., Raman, G., Trikalinos, T. A., & Lau, J. (2009). A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countries. Breastfeeding Medicine, 4(S1), S-17.
17. Hauck, F. R., Thompson, J. M., Tanabe, K. O., Moon, R. Y., & Vennemann, M. M. (2011). Breastfeeding and reduced risk of sudden infant death syndrome: a meta-analysis. Pediatrics, 128(1), 103-110.
18. Heron, M. (2007). Deaths: leading causes for 2004. National vital statistics reports, 56(5), 1-96.
19. Moon, R. Y. (2011). SIDS and other sleep-related infant deaths: expansion of recommendations for a safe infant sleeping environment. Pediatrics, 128(5), e1341-e1367.
20. Vennemann, M. M., Bajanowski, T., Brinkmann, B., Jorch, G., Yücesan, K., Sauerland, C., & Mitchell, E. A. (2009). Does breastfeeding reduce the risk of sudden infant death syndrome? Pediatrics, 123(3), e406-e410.
21. Horne, R. S., Parslow, P. M., & Harding, R. (2004). Respiratory control and arousal in sleeping infants. Paediatric Respiratory Reviews, 5(3), 190-198.
22. Kramer, M. S., Aboud, F., Mironova, E., Vanilovich, I., Platt, R. W., Matush, L., Igumnov, S., Fombonne, E., Bogdanovich, N., Ducruet, T., & Collet, J. P. (2008). Breastfeeding and child cognitive development: new evidence from a large randomized trial. Archives of General Psychiatry,65(5), 578-584.
23. Li, R., Darling, N., Maurice, E., Barker, L., & Grummer-Strawn, L. M. (2005). Breastfeeding rates in the United States by characteristics of the child, mother, or family: the 2002 National Immunization Survey. Pediatrics, 115(1), e31-e37.
24. Victora et al. The Lancet Global Health; (2013) 3(4): e199-e205.
25. Kramer, M. S. (2011). Breastfeeding and allergy: the evidence. Annals of Nutrition and Metabolism, 59(Suppl. 1), 20-26.
26. Kramer, M. S., Matush, L., Vanilovich, I., Platt, R., Bogdanovich, N., Sevkovskaya, Z., Dzikovich, I., Shishko, G., & Mazer, B. (2007). Effect of prolonged and exclusive breastfeeding on risk of allergy and asthma: cluster randomised trial. British Medical Journal, 335(7624), 815.
27. Gdalevich, M., Mimouni, D., David, M., & Mimouni, M. (2001). Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. Journal of the American Academy of Dermatology, 45(4), 520-527.
28. Dogaru, C. M., Nyffenegger, D., Pescatore, A. M., Spycher, B. D., & Kuehni, C. E. (2014). Breastfeeding and childhood asthma: systematic review and meta-analysis. American Journal of Epidemiology, kwu072.
29. Lodge, C. J., Tan, D. J., Lau, M. X. Z., Dai, X., Tham, R., Lowe, A. J., Bowatte, G., Allen, K.J., & Dharmage, S. C. (2015). Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Paediatrica, 104(S467), 38-53.
30. Garcia-Larsen, V., Ierodiakonou, D., Leonardi-Bee, J., Reeves, T., Chivinge, J., Robinson, Z., Jarrold, K., Geoghegan, N., Andreou, E., Tagiyeva-Milne, N., & Nurmatov, U. (2015). P216 Duration of total and exclusive breastfeeding, timing of solid food introduction and risk of allergic diseases: a systematic review and meta-analysis. Thorax, 70(Suppl 3), A185-A186.
31. World Health Organization (2001) Kramer, et al. Optimal duration of exclusive breastfeeding (Review)
32. Kwan, M. L., Buffler, P. A., Abrams, B., & Kiley, V. A. (2004). Breastfeeding and the risk of childhood leukemia: a meta-analysis. Public Health Reports, 119(6), 521.
33. Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2014). Prevalence of childhood and adult obesity in the United States, 2011-2012. Journal of the American Medical Association, 311(8), 806-814.
34. National Center for Health Statistics. (2012). Health, United States, 2011: With Special Features on Socioeconomic Status and Health. Hyattsville, MD; U.S. Department of Health and Human Services.
35. Arenz, S., Rückerl, R., Koletzko, B., & von Kries, R. (2004). Breast-feeding and childhood obesity—a systematic review. International Journal of Obesity, 28(10), 1247-1256.
36. Owen, C. G., Martin, R. M., Whincup, P. H., Smith, G. D., & Cook, D. G. (2005). Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. Pediatrics, 115(5), 1367-1377.
37. Harder, T., Bergmann, R., Kallischnigg, G., & Plagemann, A. (2005). Duration of breastfeeding and risk of overweight: a meta-analysis. American Journal of Epidemiology, 162(5), 397-403.
38. Baker, J. L., Michaelsen, K. F., Rasmussen, K. M., & Sørensen, T. I. (2004). Maternal prepregnant body mass index, duration of breastfeeding, and timing of complementary food introduction are associated with infant weight gain. The American Journal of Clinical Nutrition, 80(6), 1579-1588.
39. Li, C., Kaur, H., Choi, W. S., Huang, T. T. K., Lee, R. E., & Ahluwalia, J. S. (2005). Additive Interactions of Maternal Prepregnancy BMI and Breast-feeding on Childhood Overweight. Obesity Research, 13(2), 362-371.
40. Metzger, M. W., & McDade, T. W. (2010). Breastfeeding as obesity prevention in the United States: a sibling difference model. American Journal of Human Biology, 22(3), 291-296.
41. Singhal, A., & Lanigan, J. (2007). Breastfeeding, early growth and later obesity. Obesity reviews, 8(s1), 51-54.
42. Dieterich, C. M., Felice, J. P., O'Sullivan, E., & Rasmussen, K. M. (2013). Breastfeeding and health outcomes for the mother-infant dyad. Pediatric Clinics of North America, 60(1), 31-48.
43. Horta et al. Food & Nutrition Research (2013) 57: 20823
44. Gluckman et al. N Engl J Med (2008) 359, 61–73.
45. WHO Implementing the Global Strategy for Infant and Young Child Feeding: Geneva, 3-5 February 2003: (2007)
46. Lamberti et al. BMC public health. 2011; 11 Suppl 3: S15.
47. Rebhan et al. Acta Pædiatrica 2009; 98(6): 974-80.
48. Agostoni et al. J Pediatr Gastroenterol Nutr 2009; 49(1): 112-25.
49. Michaelsen et al. Gesundheitswesen 2008; 70(S 1): S20-S1.

16

Human milk: a complex system with an orchestra of functions

88% Water

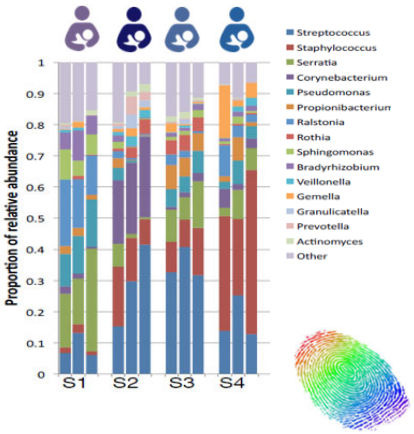
	HMOs	Bacteria & Metabolites	Fat / LCPUFA	Lactose	Proteins	Hormones	Vitamins	Living Cells	Nucleo-tides	Minerals
Immunity	●	●	●	●	●		●	●	●	
Growth	●	●	●		●	●	●		●	●
Gut Health	●	●	●	●	●	●	●	●	●	●
Other	Microbiota	Microbiota Digestion	Brain Energy	Energy	Signaling	Mood			Brain	Bone & Teeth Blood

Pereira et al., *Nutrition*, 2014;30(6):619-627.

17

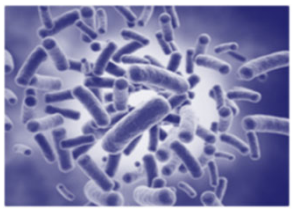
Bacteria composition of human milk (HM) is highly variable

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]



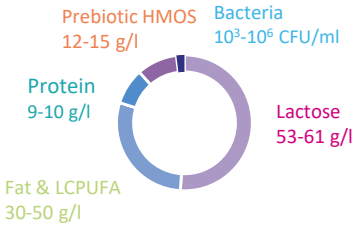
1. Hunt et al., Plos ONE: 2011; 21313.
2. Martin et al., *J Pediatrics*, 2003; 43(6):754-758.
3. Martin et al., *Applied Env Microbiol*, 2009;75(4):965-969.

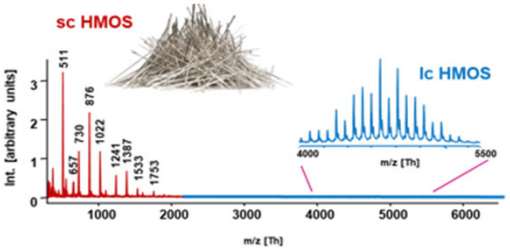
18

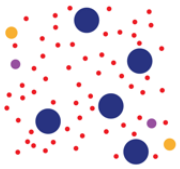
PREBIOTIC HMOs: a key component of human milk

NLC NUTRICIA LEARNING CENTER

PREBIOTIC HMOs consist of different structures with >162 identified







1000s of structures

Stahl et al., *Analyt Biochem* 1994;223:218-226.

162 structures identified

Urashima et al., *Trends Glycosci Glycotechnol* 2018;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

HMOs = human milk oligosaccharides; scHMOs = short-chain human milk oligosaccharides; lcHMOs = long-chain human milk oligosaccharides; LCPUFA = Long-chain polyunsaturated fatty acids

19

PREBIOTIC HMOs: a key component of human milk

NLC NUTRICIA LEARNING CENTER

HMOs have a multitude of functions

Prebiotic Effect: Growth and Activity of Beneficial Bacteria

- Brand-Miller et al., *J Pediatr* 1998;133:95-98.
- György et al., *Eur J Biochem*, 1974;43:29.
- Roberfroid et al., *Br J Nutr* 2010; 104:S1-63.

Brain Building Blocks

- Hart et al., *J Pediatr Psych* 2003;28:
- Wang et al., *Am J Clin Nut* 2003;78: 1024-1029.
- Stacey et al., *JACS* 2005
- Murrey et al *PNAS* 2006;103

Direct Effect on Immune Cells

- Eiwegger et al., *Pediatr Res* 2004;56:1–5.
- Bode et al., *Thromb Haem*
- 2004, 92:1402-10.
- Eiwegger et al., *PAI,* 2010; 21(8):1179-88.

Anti-Infective Effect as Receptor Analogues

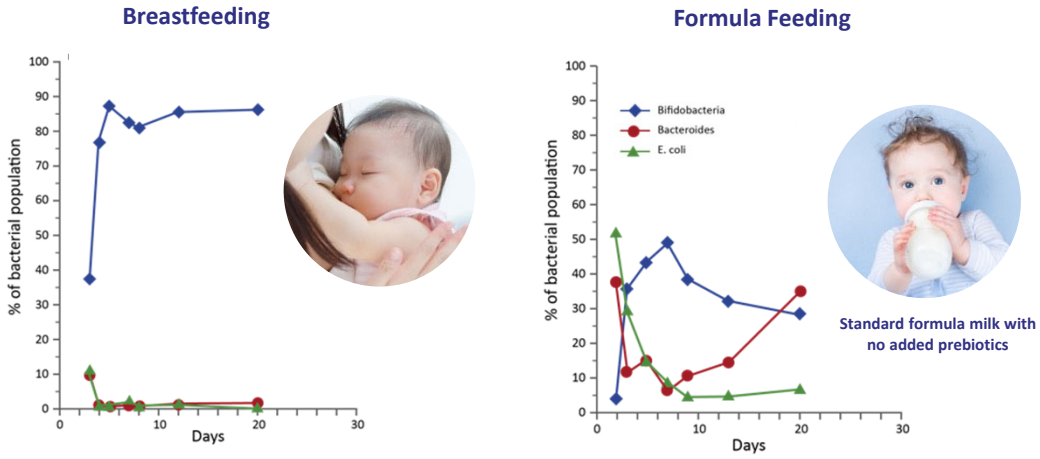
- Boehm & Stahl, In: Mattila-Sandholm T(ed): *Funct. Dairy Prod.*, 2002
- Newburg et al., *Glycobiology*, 2004, 14
- Coppa GV et al *Lancet* 1990

HMOs = human milk oligosaccharides

20

Microbiota: breast vs. bottle

HIGHER BIFIDOBACTERIA COUNT IN BABIES WHO BREASTFEED



Harmsen et al., *J Pediatr Gastroenterol Nutr.* 2000;30:61-67.

21

Synbiotics = prebiotic + probiotic

Can nutritional formulas be modified

- using a **SYNbiotic** approach -

to alter the intestinal microbiota and

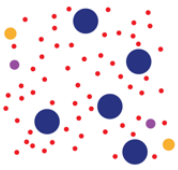
improve clinical outcomes in children?

22

Prebiotics in HM and infant formula with scGOS/lcFOS

NLC NUTRICIA LEARNING CENTER

HUMAN MILK OLIGOSACCHARIDES

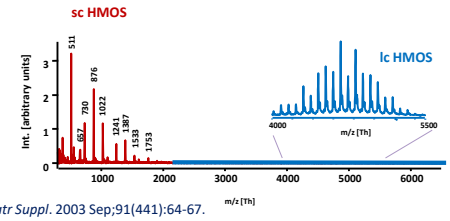


1000s of structures

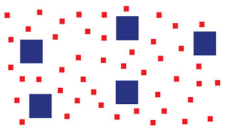
Stahl B, Thurl S, et al.
Analyt. Biochem. 1994; 223:218-226

162 structures identified

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



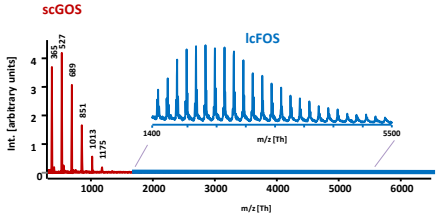
INFANT NUTRITION WITH scGOS/lcFOS (9:1)



100s of structures

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

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



Boehm et al., *Acta Paediatr Suppl*. 2003 Sep;91(441):64-67.

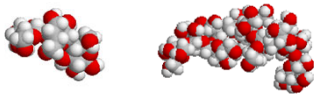
HM = human milk; scGOS = short-chain galactooligosaccharides; lcFOS = long-chain fructooligosaccharides

23

Prebiotics and Bifidogenic gut colonization

NLC NUTRICIA LEARNING CENTER

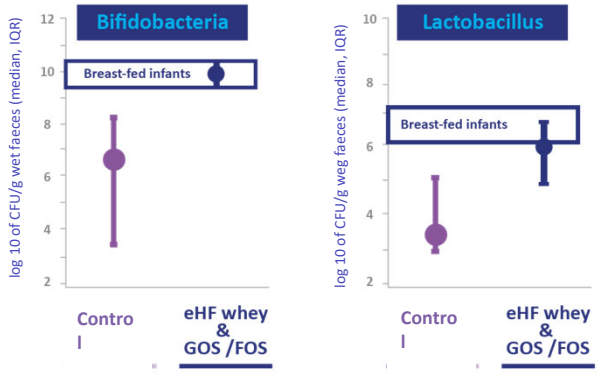
scGOS & lcFOS



- 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., *World Gastroenterol* 2014

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



Moro et al., *J Ped Gastroenterology & Nutrition* 2002

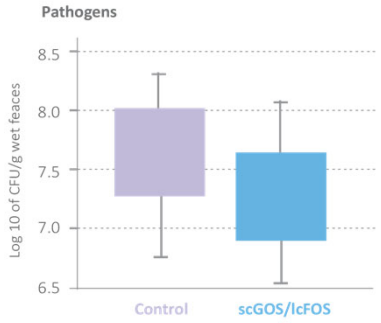
24

scGOS/lcFOS supports intestinal 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 Paediatrica;94 (Suppl 449):31–33.

scGOS = short-chain galactooligosaccharides; lcFOS = long-chain fructooligosaccharides

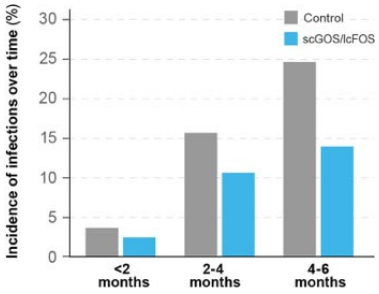
25

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. J Nutr 2007;137:2420-2424.

scGOS = short-chain galactooligosaccharides; lcFOS = long-chain fructooligosaccharides

26

scGOS/lcFOS reduces infections and incidence of allergic manifestations during the first 2 years of life

Target population
Healthy infants

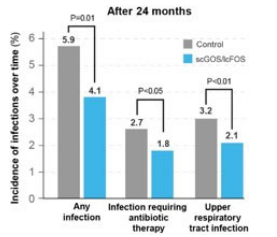
Conclusions

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.

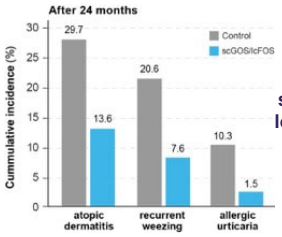
Study design

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. J Nutr 2008;138:1091-1095

scGOS = short-chain galactooligosaccharides; lcFOS = long-chain fructooligosaccharides; URTI = upper respiratory tract infections

27

scGOS/lcFOS reduces intestinal infections

Target population
Healthy infants

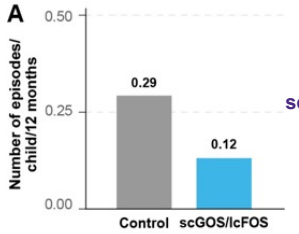
Conclusions

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

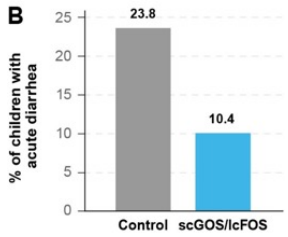
Study design

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. *Clinical Nutrition* 2009;28:156-161

scGOS = short-chain galactooligosaccharides; lcFOS = long-chain fructooligosaccharides

28

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

NLC NUTRICIA LEARNING CENTER

maximal allergen elimination

- Hypoallergenic formula
- Protein source: 100% amino acids
- 0-12 months of age

helps to address underlying gut dysbiosis

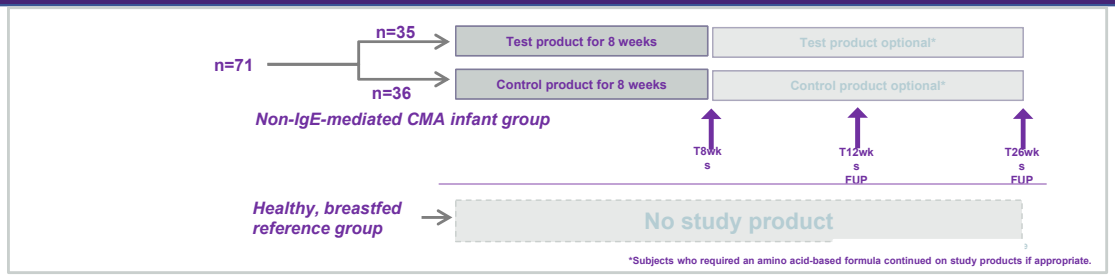
- **sc-FOS / lc-FOS** (9:1 ratio)
- 0.63g / 100 ml
- no GOS, to avoid cow milk protein contamination

- ***Bifidobacterium breve* M-16V**
- 10^8 *CFU*/g powder
- processed in a milk-free environment

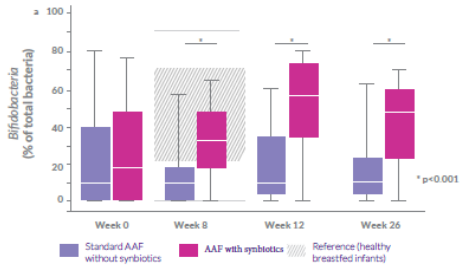
29

AAF + specific synbiotic blend promotes sustained bifidobacteria growth and reduces *Eubacterium / Clostridia*, similar to breastfed infants

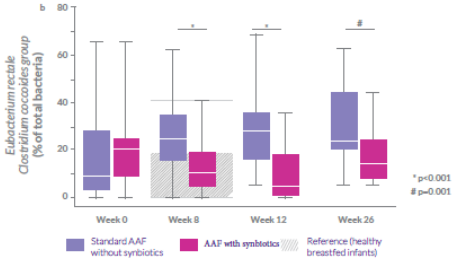
NLC NUTRICIA LEARNING CENTER



***Bifidobacterium* species in fecal microbiota**



***E. rectale / C. coccoides* cluster in fecal microbiota**



Fox, et al. Clin Transl Allergy. 2019;9:5.

AAF = amino acid-based formula

30

Recent meta-analysis of AAF + specific synbiotic blend

Lead Author (Date)	Population and Type of Study	Male	Mean Age (Months)	Amount of Formula Consumed/Day (mL) Mean ± *SD*	*n* AAF-Syn	*n* AAF	Intervention Duration	Timepoint Outcomes Measured
Harvey (2014) [38] Full paper	Infants with IgE mediated CMPA aged 0–36 months One arm DBPCCFC and 7 day feeding period	61%	17.3, range 3.3–46.9	Not reported	30	30	7 days	7 days
	Full-term healthy infants aged 3–16 months, RCT ¶	*67%*	*10.6, range 3–16*	*AAF-Syn: 349 ± 127* §; *AAF: 331 ± 124* §	*59*	*56*	*16 weeks*	*2, 4, 8, 12 & 16 weeks*
Burks (2015) [39] Full paper	Infants with IgE or non-IgE mediated CMPA aged 0–8 months, RCT	62%	4.5, range 0.6–8.9	Not reported. Intake was reported as comparable in both groups	54	56	16 weeks	4 & 16 weeks
Candy (2018) [32] ASSIGN study, full paper	Infants with non-IgE mediated CMPA aged 0–13 months, RCT Included breast-fed healthy reference group (not randomised)	73%	6, range 1.2–12.8	Week 8 AAF-Syn 652 ± 176; AAF 639 ± 212	35	36	8 weeks	4 & 8 weeks
Fox (2019) [33] † ASSIGN study, full paper	Infants with non-IgE mediated CMPA aged 0–13 months 26-week follow-up of Candy (2018)	73%	6, range 1.2–12.8	Week 8 AAF-Syn 652 ± 176; AAF 639 ± 212	35	36	8 weeks	8, 12 & 26 weeks
Wopereis (2019) [40] † ASSIGN study, full paper	Infants with non-IgE mediated CMPA aged 0–13 months Gene-sequencing analysis from Candy (2018) and Fox (2019)	73%	6, range 1.2–12.8	Week 8 AAF-Syn 652 ± 176; AAF 639 ± 212	35	36	8 weeks	8, 12 & 26 weeks
Chatchatee (2019) [31] PRESTO study ‡, conference abstract	Infants with confirmed IgE mediated CMPA aged 0–13 months, RCT	72%	9.36, SD 2.53	At 12 months: AAF-Syn: 547 ± 302; AAF: 530 ± 308	80	89	12 months	12 months
Wopereis (2020) [30] PRESTO study ‡, conference abstract	Infants with confirmed IgE mediated CMPA aged 0–13 months, RCT							

CMPA: cow's milk protein allergy; RCT: randomised controlled trial; DBPCCFC: double blind placebo-controlled crossover food challenge; AAF-Syn: amino acid formula with synbiotics (Neocate Syneo®, Nutricia); AAF (control): amino acid formula (Neocate LCP®, Nutricia); † original RCT (Candy 2018 [32]) was for 8 weeks, Fox (2019) [33] and Wopereis (2019) [40] were published after original RCT; ‡ Chatchatee (2019) [31] and Wopereis (2020) [30] report different outcomes from same study; § Converted from reported oz/d (11.8 ± 4.3 oz/d AAF-Syn; 11.2 ± 4.2 oz/d AAF); ¶ Included in table for completeness, but outside scope of review as subjects were not required to have CMPA.

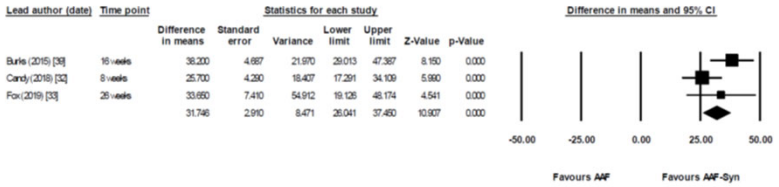
Sorensen et al., Nutrients, 2021;13:935-954.

AAF = amino acid-based formula

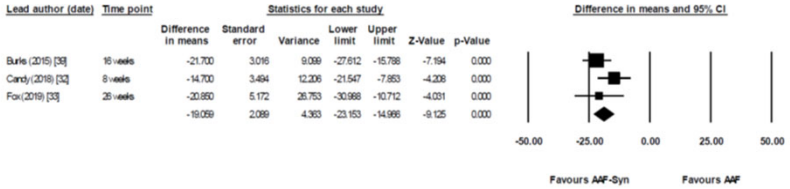
31

Meta-analyses reveal consumption of AAF + specific synbiotic blend enhance microbiota community

- increased percentages of faecal bifidobacterial species with AAF-Syn



- lower percentages of adult-like *Eubacterium rectale* and *Clostridium coccoides* species with AAF-Syn

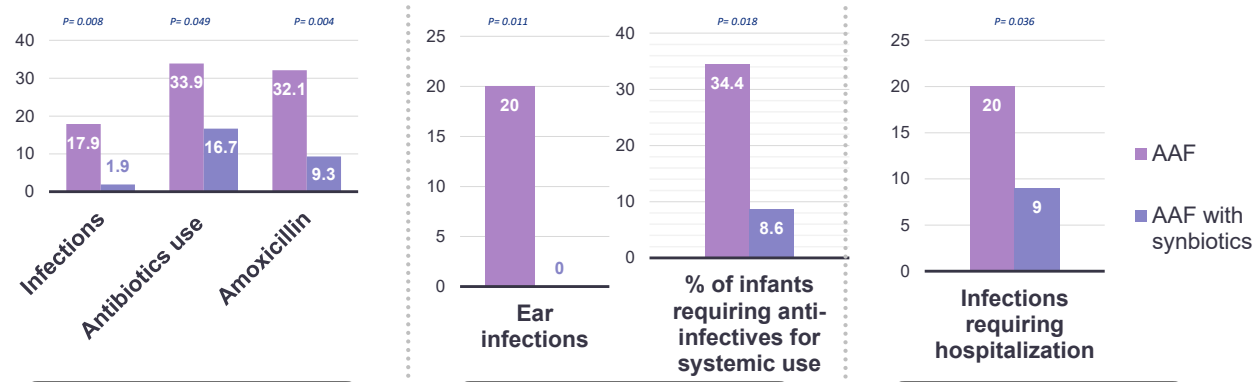


Sorensen et al., Nutrients, 2021;13:935-954.

AAF = amino acid-based formula

32

Evaluation of adverse events: 3 RCTs with AAF with synbiotics show a reduction in reports of infections & antibiotic usage



Fewer reported infections and use of antibacterial for systemic use, specifically amoxillin[1]

Fewer reported ear infections and use of anti-infectives[2,3]

Fewer reported infections requiring hospitalization[4]

1. Burks, et al. Pediatr Allergy Immunol. 2015;26:316-22.
2. Candy, et al. Pediatr Res. 2018;83:677-86.
3. Fox, et al. Clin Transl Allergy. 2019;9:5.
4. Chatchatee, et al. J Allergy Clin Immunol. 2022;149:650-8.e5.

AAF with synbiotics includes: scFOS/lcFOS & B.*breve* M-16V

RCTs = randomized controlled trial; AAF = amino acid-based formula

33

Multiple studies demonstrate consumption of AAF with synbiotics improve clinical outcomes

- Compared to AAF, significantly fewer infants fed AAF-Syn had infections*
- Overall medication* use, including antibacterials and anti-infectives, was lower among infants fed AAF-Syn.
- Significantly fewer infants had hospital admissions (arising from infections) with AAF-Syn compared to AAF (8.8% vs. 20.2%, p = 0.036; 56% reduction), leading to potential cost savings† per infant of £164.05–£338.77.

* Exploratory findings, from component studies (not powered to test these outcomes), were the results of safety evaluations. † Cost savings based on UK hospital admission costs. Costs may vary in the US.

Sorensen et al., Nutrients, 2021;13:935-954.

AAF = amino acid-based formula

34

Conclusion

Nutritional strategies employing
PRObiotics + 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.

35

We need to consider (and feed) the complex ecosystem

36

We appreciate your feedback!
Certificate of Attendance

NLC
NUTRICIA LEARNING CENTER

1. Please provide feedback through the survey - 3 ways to access:

Aim your smartphone camera at this → QR code

OR
access the survey at:
www.surveymonkey.com/r/CMAGM2

OR
after live event: survey in post-event email and pops up when you exit

To receive your certificate of attendance:

2. Find the **event code** at end of survey

3. Visit www.NutriciaLearningCenter.com
Enter **event code** into your NLC Dashboard
Certificate of Attendance added to your NLC profile!

Nutricia Learning Center is provided by Nutricia North America
For questions on this webinar or Nutricia's products, please email: NutritionServices@nutricia.com or call: **1-800-365-7354**

37