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NEW JERSEY ACADEMY of Nutrition and Dietetics

Virtual CE-eligible Education Program

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

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Tuesday, May 18th, 2021

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Dr. Kelly Tappenden is Professor and Head of the Department of Kinesiology and Nutrition at the University of Illinois at Chicago. She has received multiple awards, published over 100 peer-reviewed papers, and delivered over 400 invited lectures. Dr. Tappenden has lectured across the US sharing her expertise and unique insights related to the Role of the Gut Microbiota, Pre – Probiotics in the Management of Pediatric Allergy. She has served as the 33rd President of the American Society for Parenteral and Enteral Nutrition in 2008-09, Chair of the Nutrition, Metabolism and Obesity section of the American Gastroenterology Association Institute from 2009-13, and presently represents the American Society for Nutrition on the Federation of American Societies for Experimental Biology. Dr. Tappenden has been the Editor-in-Chief of the Journal for Parenteral and Enteral Nutrition since 2010.

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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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Learning Objectives

1. Explain the importance of the gut microbiota in early life and the development of the immune system;
2. Explore the role of specific probiotics and prebiotics in the dietary management of infants with cow milk allergy;
3. Examine tips for the practicing RD based on a growing body of evidence.

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Audience Poll

1. Are you currently using prebiotics and/or probiotics in your clinical practice?
   - A. Yes - prebiotics
   - B. Yes - probiotics
   - C. Yes – both pre- and probiotics
   - D. No

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Audience Poll

2. The gut microbiota in infancy supports digestion and impacts maturation of the immune system.
   - A. Strongly Agree
   - B. Agree
   - C. Don't know
   - D. Disagree
   - E. Strongly disagree

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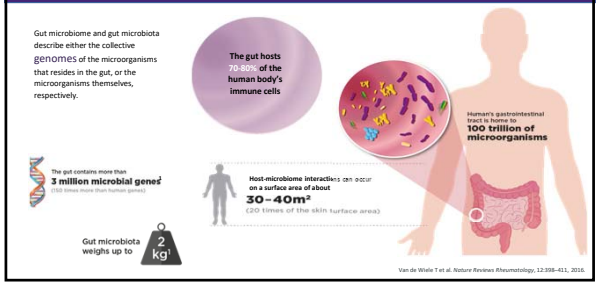
The Intestinal Microbiota



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Why is intestinal microbiota important?

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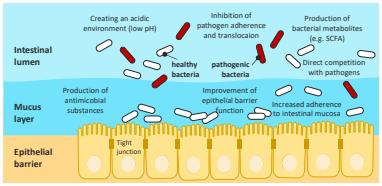
The gut microbiota acts as a barrier against pathogens

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

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



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

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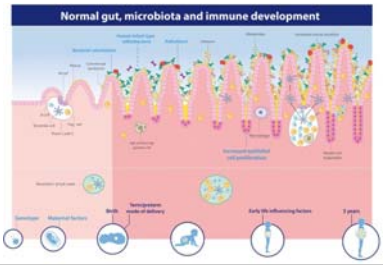
Development of the immune system starts with the intestinal microbiota



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

Immune maturation depends on gut microbiota signals.

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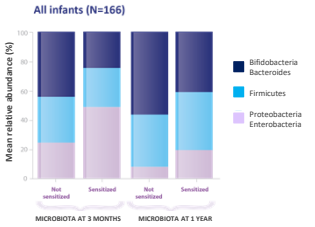
A HEALTHY GUT MICROBIOTA SUPPORTS ORAL TOLERANCE

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 et al., 2015. Clinical and Experimental Allergy

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Dysbiosis preceeds 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.

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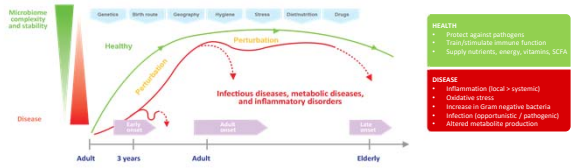
Factors affecting stability and complexity of gut microbiome in health and disease



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

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Several factors affect early gut microbiota development

EARLY LIFE IS A WINDOW OF OPPORTUNITY

WINDOW OF OPPORTUNITY FOR MICROBIOTA MODULATION

Pregnancy
- Minimal exposure via placenta
- Maternal factors: Stress, diet in late pregnancy, BMI, smoking and socioeconomic status

Birth
- Mode of delivery
- Gestational age

Early infancy
- Diet: breast-milk vs. formula
- Antibiotics
- Proton pump inhibitors

Late infancy
- The introduction of solid foods
- Various insoluble indigestible carbohydrates
- Antibiotics
- Proton pump inhibitors

PHYSIOLOGICAL FACTORS - ENVIRONMENT - DIET - CULTURAL FACTORS - GEOGRAPHICAL LOCATION - ANTIBIOTIC USE
DISEASE - FAMILY SIZE AND SITUATION - STANDARD OF SANITATION

Marques AH, *Frontiers in Neuroscience*. 2013 Jul 31;7:120.

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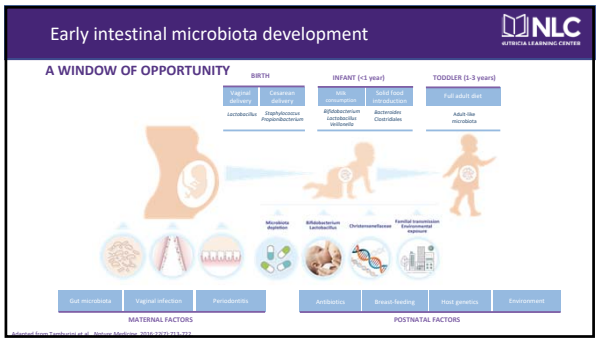
Early intestinal microbiota development



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

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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., 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.

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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

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

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Bacteria Composition of Human Milk is highly variable

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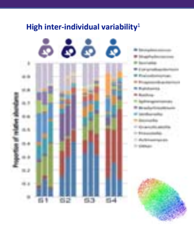
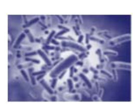


HM contains 10^3-10^5 Colony Forming Units/ml bacteria, including Lactobacilli, Bifidobacterium and Staphylococcus.[1-3]



Lactic acid bacteria in human milk ≠ Vagina or skin of the mother.[2]

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2. Martin et al., *J Pediatrics*, 2003; 43(6):754-758.
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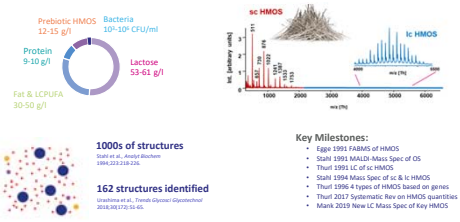
PREBIOTIC HMOs: a key component of human milk

PREBIOTIC HMOs consist of different structures with >162 identified



1000s of structures

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

162 structures identified

Urashima et al., *Trends Glycosci Glycotechnol* 2018;30:SE51-65.

Key Milestones:

- Egge 1991 FABMS of HMOS
- Stahl 1991 MALDI-Mass Spec of OS
- Thuil 1991 LC of sc HMOS
- Stahl 1994 Mass Spec of sc & lc HMOS
- Thuil 1996 4 types of HMOS based on gones
- Thuil 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

- Brand-Miller et al., *J Pediatr* 1998;133:95-98.
- Gyorgy et al., *Eur J Biochem*, 1974;43:29.
- Roberfroid et al., *Br J Nutr* 2010; 104:51-63.

Brain Building Blocks

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

Direct Effect on Immune Cells

- Ewaggar et al., *Pediatr Res* 2004;56:1–5.
- Bode et al., *Thromb Haem* 2004, 92:1402-10.
- Ewaggar et al., *PAL* 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

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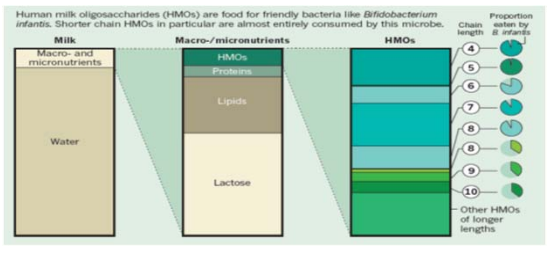
Human milk = the ultimate **SYNbiotic**!



Petherick *Nature* 2010;65:S5-S7

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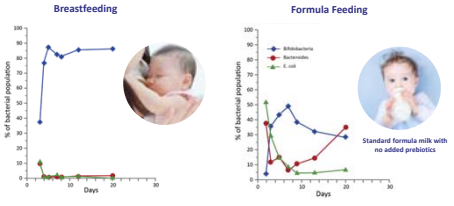
Microbiota: breast vs bottle

HIGHER BIFIDOBACTERIA COUNT IN BABIES WHO BREASTFEED



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

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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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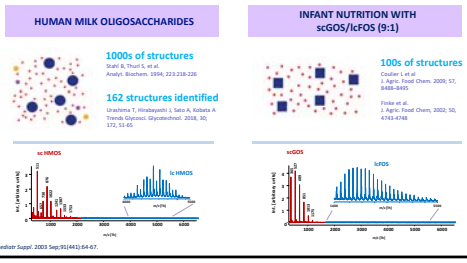
Prebiotics in HM and infant formula with scGOS/lcFOS



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

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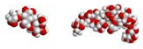
Prebiotics and Bifidogenic gut colonization

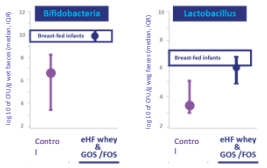
scGOS & lcFOS



- 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., *World Gastroenterol* 2014

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



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

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scGOS/lcFOS supports MICROBIOTA by discouraging the growth of potential pathogens

Target population Preterm

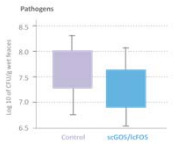
Conclusions

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 Paediatrica, 2004;94 (Suppl 449):31–33.

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scGOS/lcFOS reduces infections during the first 6 months of life

Target population Healthy infants

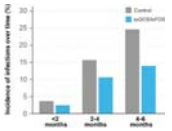
Conclusions

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. J Nutr 2007;137:2420-2424.

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

Target population Healthy infants

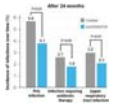
Conclusions

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.

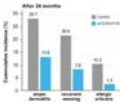
Study design

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

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scGOS/lcFOS reduces intestinal infections

Target population Healthy infants

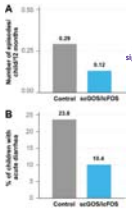
Conclusions

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

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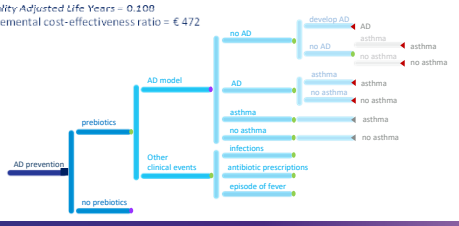
USE of formula with scGOS/lcFOS prebiotics result in positive short- and long-term health economic benefits

- Prebiotic cost = €51
- *Quality Adjusted Life Years* = 0.100
- Incremental cost-effectiveness ratio = € 472



Lenoir-Wijnkoop et al., *Eur J Health Econ* 2012;13:101–110.

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Amino acid-based formula (AAF) with specific synbiotics aims to eliminate allergens for active management of cow 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**
- 10^8 *CFU*/g powder
- processed in a milk-free environment

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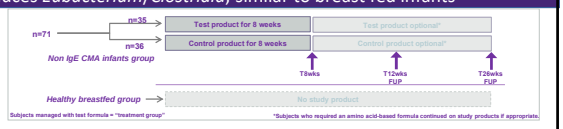
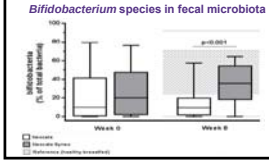
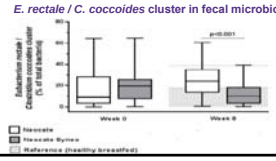
AAF + specific synbiotics promotes *bifidobacteria* growth and reduces *Eubacterium/Clostridia*, similar to breast fed infants



***Bifidobacterium* species in fecal microbiota**



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



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Recent meta-analysis of AAF+Syn

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) [39] Full paper	Infants with IgE mediated CMPA aged 0–36 months; One arm DBPCCFC and 7 day feeding period	61%	17.5, range 3.5–40.9	Not reported	30	30	7 days	7 days
	Full-term healthy infants aged 3–26 months, RCT [§]	67%	10.6, range 3–26	AAF-Syn: 349 ± 127 [¶]; AAF: 332 ± 128 [¶]	39	36	26 weeks	2, 4, 8, 12 & 26 weeks
Berko (2015) [38] 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	34	36	16 weeks	4 & 16 weeks
Candy (2016) [32] ASMGN 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 452 ± 176; AAF 439 ± 252	33	36	8 weeks	4 & 8 weeks
Fox (2019) [33] [#] ASMGN study, full paper	Infants with non-IgE mediated CMPA aged 0–13 months. 26-week follow-up of Candy (2016)	73%	6, range 1.2–12.8	Week 8 AAF+Syn 452 ± 176; AAF 439 ± 252	33	36	8 weeks	8, 12 & 26 weeks
Wopereis (2019) [40] [#] ASMGN study, full paper	Infants with non-IgE mediated CMPA aged 0–13 months. Gene-sequencing analysis from Candy (2016) and Fox (2019)	73%	6, range 1.2–12.8	Week 8 AAF+Syn 452 ± 176; AAF 439 ± 252	33	36	8 weeks	8, 12 & 26 weeks
Chatchatee (2019) [31] PREDO study [‡], conference abstract	Infants with confirmed IgE mediated CMPA aged 0–13 months, RCT	72%	9.36, SD 2.51	At 12 months: AAF+Syn: 747 ± 302; AAF: 750 ± 309	40	40	12 months	12 months
Wopereis (2020) [34] PREDO 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 consecutive food challenge; AAF+Syn, amino acid formula with synbiotics (Neocate Syneo®, Nutricia); AAF (control), amino acid formula (Neocate LCP®, Nutricia); [‡] original RCT (Candy 2016 [32]) was for 8 weeks, Fox (2019) [33] and Wopereis (2019) [40] were published after original RCT; [§] Chatchatee (2019) [31] and Wopereis (2020) [34] report different outcomes from same study; [¶] Converted from reported oz (AAF+Syn: 13.2 ± 4.3 oz; AAF: 11.7 ± 4.5 oz); [#] 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.

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Meta-analyses reveal consumption of AAF+Syn 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.

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Multiple studies demonstrate consumption of AAF+Syn improve clinical outcomes

- Compared to AAF, significantly fewer infants fed AAF-Syn had infections*
- Overall medication* use, including antibacterials and antifectives, 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.

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

* 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.

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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.

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We need to consider (and feed) the complex ecosystem

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We appreciate your feedback! Certificate of Attendance

For those interested in obtaining a Certificate of Attendance:

1) Please complete the survey by visiting the link OR open the camera on your smartphone and hold over the QR code.
   - https://www.surveymonkey.com/r/NEKTGMCMA
   - An event code will be available at the end of the survey.
2) Go to www.NutriciaLearningCenter.com and enter the event code by visiting 'My NLC Dashboard' – 'My CE credits'. Your certificate will be automatically downloaded to your NLC profile.

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Thank you!

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