Are Children with Cow's Milk Allergy More Prone to Illness? A Look at the Latest Information

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Disclosures

Honorarium academic lectures:
- Nutricia/Danone
- Reckitt Benckiser Group
- Nestle Nutrition
- Abbott

Allergy boards:
- Abbott Nutrition
- CoMISS board: Nestle Nutrition

Research grants:
- Nutricia/Danone

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

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Objectives

1. Summarize data on the immune system and infections in children with cow's milk allergy (CMA)
2. Illustrate the possible cause of infections in children with CMA
3. State possible CMA dietary management options and future research

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Do you think that children with a CMA have more frequent Illness?

1. Yes
2. No

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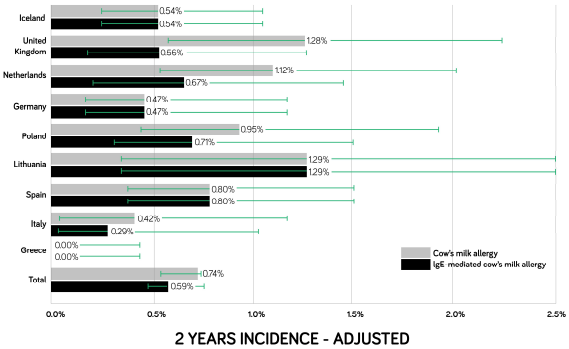
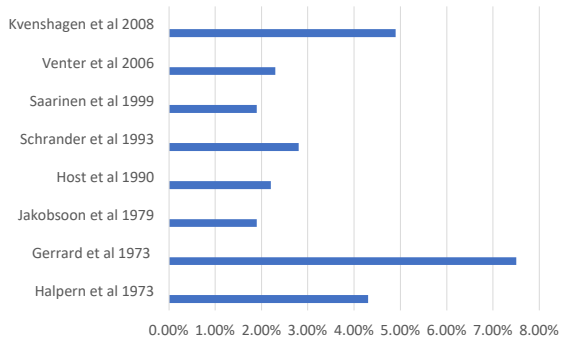
Prevalence of Cow's Milk Allergy (CMA)

- The EuroPrevall study: based on DBPCFC in 12,000 infants (24-30 months) showed an overall prevalence of 0.59%, ranging from 0-1.3% in different countries.





- Concern was expressed about prevalence (recognition) of non-IgE-mediated allergies: UK had the highest rate of non-IgE-mediated allergies at 0.72%
- Luyt et al. 2014 – prevalence 1.8-7.5%

Schoemaker et al. Allergy 70 (2015) 963–972
Luyt et al. Clinical & Experimental Allergy, 44, 642–672.
Heine & Koletzko. Allergy 70 (2015) 1679–1680 5

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Symptoms of CMA – but what about infections?

	Symptoms in infant and toddlers
Digestive	Dysphagia Frequent regurgitation Colic, abdominal pain Vomiting Anorexia, refusal to feed Diarrhea +/- intestinal protein or blood loss Constipation +/- perianal rash Failure to thrive Occult blood loss iron-deficiency anemia
Respiratory	Runny nose Wheezing Chronic coughing (all unrelated to infections)
Skin	Urticaria (unrelated to infections, drug intake, or other causes) Atopic eczema Angioedema (swelling of lips or eyelids)
General	Anaphylaxis Shock-like symptoms with severe metabolic acidosis, vomiting, and diarrhea (FPIES)

GI infections?

Respiratory infections and ear infections

Skin infections

Fiocchi et al. WAO Journal, April 2010
Awaiting new WAO guidelines – to be published in 2022

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The clinical burden of cow's milk allergy in early childhood: A retrospective cohort study

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Katy Sorensen[1] | Rosan Meyer[2] | Kate E. Grimshaw[3,4] | Abbie L. Cawood[1,4] | Dionisio Acosta-Mena[5] | Rebecca J. Stratton[1,4]

- A retrospective, observational study comparing clinical and healthcare outcomes among children with CMA and those without
- Data generated from the THIN database

n=6998
CMA (n=3499) vs non-CMA (n=3499)

Inclusion criteria	Exclusion criteria
- Male or female - Diagnosed with CMA and/or prescribed HAF in the last 4y 11m - Age of diagnosis and/or first prescription of a HAF ≤12m - Have received at least 3 prescriptions (3m) of HAF - Patient record flagged as 'acceptable' according to THIN	Metabolic conditions, intestinal failure, necrotizing enterocolitis, cancer/ malignancy/ tumor, cardiology, cystic fibrosis, cerebral palsy and chromosomal anomalies, patients on 'other' prescribed medical nutrition not indicated for CMA

THIN = The Health Improvement Network; HAF = Hypoallergenic formula
Sorensen et al. Immun Inflamm Dis. 2021;1–11. Open Access

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TABLE 4 Differences in occurrence of infections in the CMA versus non-CMA cohort

	CMA ($n = 3499$)	Non-CMA ($n = 3499$)	p-value
GI infections			
n (%)[a]	282 (8.1)	162 (4.6)	<.001
Infection rate[b]	0.105	0.065	<.001
Skin infections			
n (%)[a]	1898 (54)	1584 (45)	<.001
Infection rate[b]	1.305	0.955	<.001
Respiratory infections			
n (%)[a]	3098 (89)	2854 (82)	<.001
Infection rate[b]	6.88	5.03	<.001
Ear infections			
n (%)[a]	875 (25)	673 (19)	<.001
Infection rate[b]	0.51	0.355	<.001

- **GI infections:** viral gastroenteritis, gastroenteritis of other presumed infectious origin, campylobacter GI infection, and diarrhea and vomiting caused by suspected infection
- **Skin infections:** skin and subcutaneous tissue infections.
- **Respiratory infections:** upper respiratory tract infection and acute tonsilitis
- **Ear infections:** otitis media, infective otitis externa, and ear pain

Sorensen et al. Immun Inflamm Dis. 2021;1–11. Open Access

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CMA and Ear Infections

- **Juntti et al 1999**: 108 children who were on the Finnish public insurance database with documented CMA. From these only the children with confirmed (challenged) CMA and still in the area were enrolled (n = 56) and were invited for a review and completed the questionnaire on otitis media.

No respiratory atopy (n = 180)			
	CMA	Controls	*p*-value
Recurrent otitis	14%	12%	0.73
Adenoidectomy for ear problems	24%	23%	1.00
Tympanostomy	19%	12%	0.32
Secretory otitis media	5%	9%	1.00

Respiratory atopy (n = 80)			
	CMA	Controls	*p*-value
Recurrent otitis	34%	13%	0.03
Adenoidectomy for ear problems	51%	22%	0.009
Tympanostomy	37%	16%	0.04
Secretory otitis media	24%	16%	0.39

Juntti et al. Acta Oto- Laryngologica, 119:8, 867-873. Open Access. Soares de Oliveira et al. Brazilian Journal of Otorhinolaryngology 2021 Article in Press

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CMA and Ear Infections

- **Juntti** … urance … th … = 56) … otitis media.

Soares de Oliveira et al. Systematic review on Recurrent Ear Infections (ROM) and CMA

"Observational studies were identified, which showed considerable heterogeneity regarding the methodological design, age group of the studied population and diagnostic methods for CMA and otitis media. Thus, the results found in this review do not allow us to state that there is a correlation between CMA and the development of ROM"

			p-value
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CMA and Respiratory Infections

- **Meyer et al 2013:** retrospective study in non-IgE-mediated food allergy
  - 67% of children had frequent respiratory infections (defined > 1 infection per month)
- **Ciprandi et al 2006:** prospective study
  - 117 children included and studied during spring.
    - 46/117 were allergic (39%)
  - Average age 4.02 ± 1.0 yr, (72 males and 45 females) were studied during the spring
  - Allergic children had significantly higher number (mean 1.26 ± 0.73) and longer duration of respiratory infections (8.92 days) in comparison with non-allergic group (0.94 ± 1.37 and 4.85 days)

Meyer et al. World Allergy Organization Journal 2013, 6:13
Ciprandi et al. Pediatr Allergy Immunol. 2006;17(5):389-391.

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Can something be done about the frequent illness?

1. Yes

2. No

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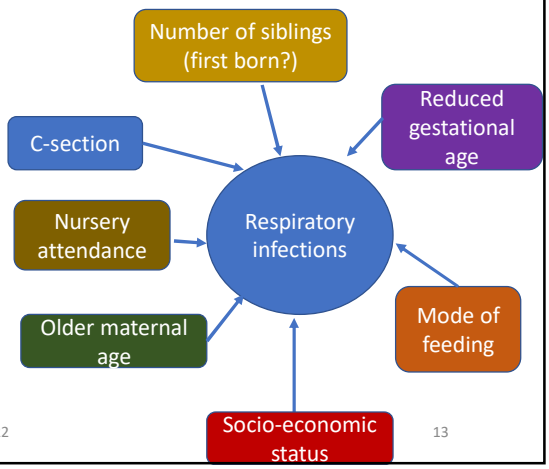
Review

Early-Life Respiratory Infections in Infants with Cow's Milk Allergy: An Expert Opinion on the Available Evidence and Recommendations for Future Research

Alessandro Fiocchi [1], Jan Knol [2,3], Sibylle Koletzko [4,5], Liam O'Mahony [6], Nikolaos G. Papadopoulos [7,8], Seppo Salminen [9], Hania Szajewska [10] and Anna Nowak-Węgrzyn [5,11,*]

- Acknowledge that there was limited data on the prevalence and severity of infections in infants with CMA
- Some studies in infants with CMA have reported higher rates of respiratory infections.
- Infants with a predisposition to atopy have delayed maturation of the Th1 response during childhood, putting them at increased risk for infection in the first years of life.



Fiocchi et al. Nutrients 2021, 13, 3795. Open access

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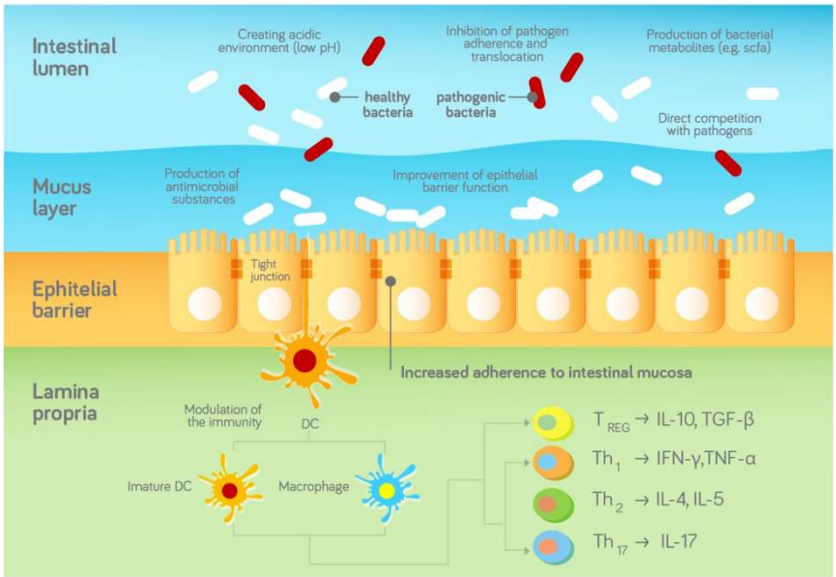
Can Gut Microbiota Support the Immune System ?



- Competition for adhesion sites and nutrients
- Production of bacterial metabolites such as SCFA
- Creating an acidic environment
- Production of antimicrobial substances such as antimicrobial peptides
- Supporting the epithelial and mucosal barrier.

SCFA = short-chain fatty acids

Fiocchi et al. Nutrients 2021, 13, 3795. Open access

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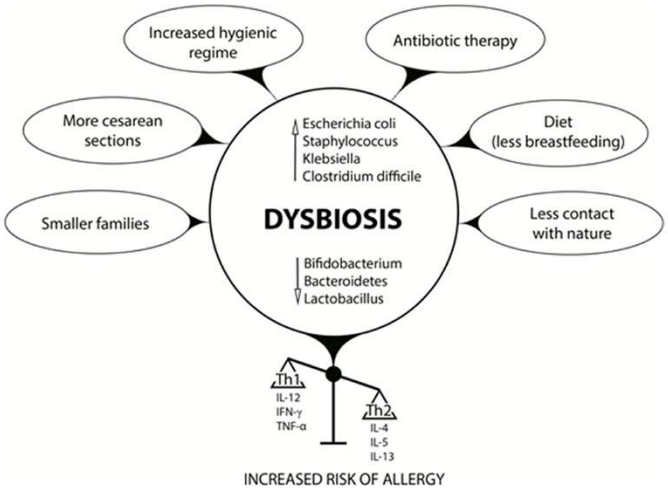
Could Gut Dysbiosis Contribute Towards Increased Infections?



Cukrowska et al. Nutrients 2020, 12, 946. Open Access

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Gut Microbiota in Immune Response and Food Allergy

Gut microbiota changes dramatically during the first year of life and is relatively stable and mature after 3 years of age

- developmental phase (months 3–14)
- transitional phase (months 15–30),
- stable phase (months 31–46)

In allergic infants, several studies show the presence of altered gut microbiota, or 'dysbiosis' (a breakdown in the balance of intestinal bacteria)

- *Bifidobacteria* are the first colonisers of healthy infant gut
- Children with CMA have lower gut microbiota diversity
- Infants with IgE-mediated allergy typically have low levels of *Bifidobacteria*
- Children with non-IgE-mediated allergy have dysbiosis driven by *Bacteroides and Alistipes*
- Composition of gut microbiota at age 3–6 months was associated with CMA by the age of 8 years with the enrichment of class Clostridia and phylum Firmicutes in the infant's gut microbiota

Moos W, et al. Biores Open Access. 2017 May 01; 6(1): 46.. Tamboli C, et al. Gut. 2004 Jan; 53(1): 1–4.. Thompson-Chagoyan OC, et al. Int Arch Allergy Immunol 2011; 156: 325-332. Kirjavainen PV, et al. Gut 2002; 51: 51–55. Soto A, et al. J Pediatr Gastroenterol Nutr. 2014 Jul; 59(1): 78–88.. Canani et al. Sci Rep. 2018 Aug 21;8(1):12500.. Dong et al. Saudi J Biol Sci. 2018 Jul;25(5):875-880. Bunyavanich et al. *J. Allergy Clin. Immunol.* 2016;138:1122–1130. Petersen et al. *Cell Rep. Med.* 2:100260.

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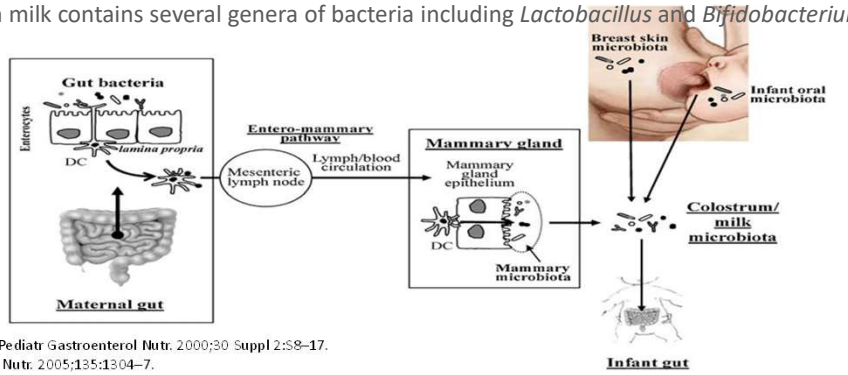
Breast Milk = Rich Source of Pre- and Probiotics

- Breastfed infants develop an intestinal flora dominated by *Bifidobacteria* and *Lactobacilli* with less pathogenic bacteria compared with formula-fed infants
- Human milk oligosaccharides are an important components of the defense system of human milk, in particular due to its prebiotic effect
- Human milk contains several genera of bacteria including *Lactobacillus* and *Bifidobacterium*



1. Newburg DS. J Pediatr Gastroenterol Nutr. 2000;30 Suppl 2:S8–17.
2. Morrow et al. J Nutr. 2005;135:1304–7.
3. Hunt et al. PLoS ONE 6(6): e21313. doi:10.1371.
4. Milani et al. Microbiology and Molecular Biology Reviews 2017;81:1-64
5. Fernández L, et al. Pharmacol Res. 2013;69:1-10

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Breastfeeding Can Protect Against Infections

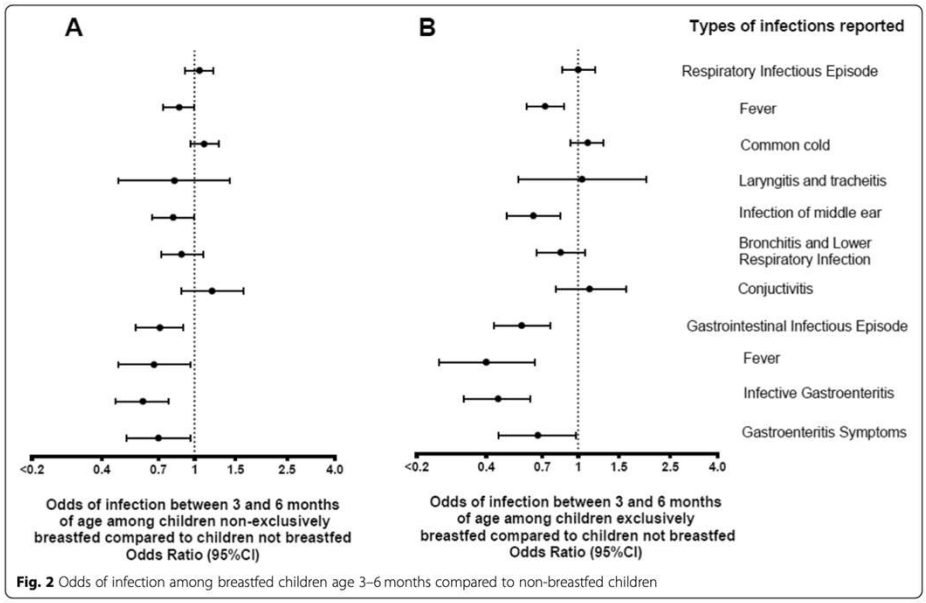

Fig. 2 Odds of infection among breastfed children age 3–6 months compared to non-breastfed children

Frank et al. BMC Pediatrics (2019) 19:339. Open Source - http://creativecommons.org/licenses/by/4.0

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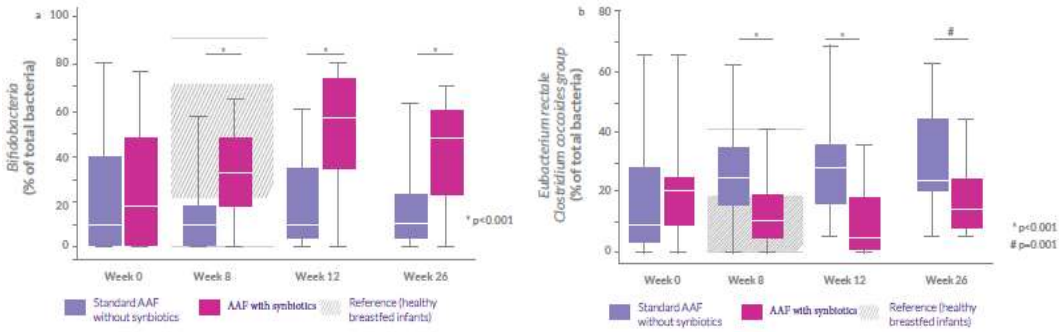
Effect of Synbiotics on Gut Dysbiosis in CMA

- *Fox et al 2019 (ASSIGN):*
  - A hypoallergenic[1] amino acid-based formula (AAF) + synbiotics (short & long chain fructooligosaccharides [scFOS/lcFOS] & *B. breve* M-16V) shown to bring the gut microbiota closer to that of healthy breastfed infants vs standard AAF.



Increased level of infant-like Bifidobacteria

Decrease of adult-like E. rectale/ C. coccoides cluster

Fox et al. Clin Transl Allergy (2019) 9:5

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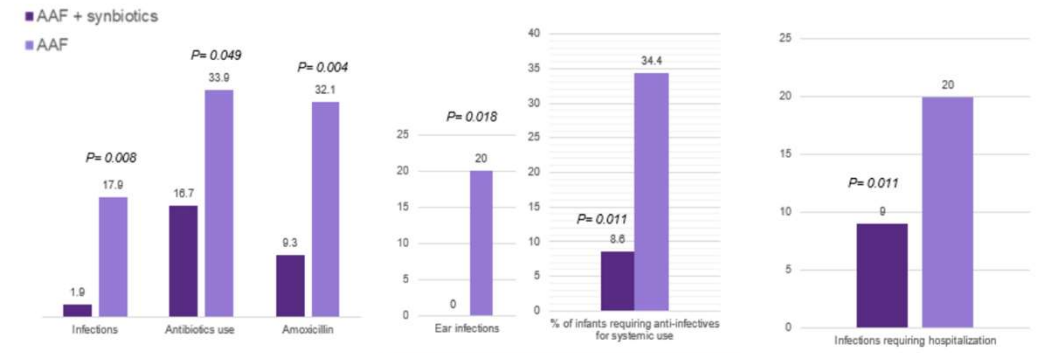
Impact of Synbiotics on Infections in CMA



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

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

Fewer 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.

Exploratory findings are results of safety evaluations and do not intend to offer final and conclusive results. Further research is needed to confirm the findings.

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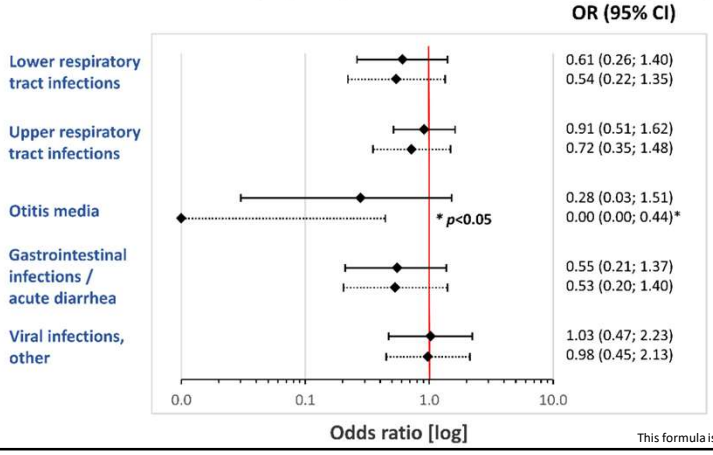
Impact of HMO on Infections

- Assessed a new 100% whey-based EHF supplemented with HMO: 2'-fucosyllactose (1.0 g/L) and lacto-N-neotetraose (0.5 g/L)
- Recruited 94 infants in the study group and 96 in the control group



Vandenplas et al. Nutrients 2022, *14*, 530.

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This formula is not currently available in North America.

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Effect of Synbiotics on Concomitant Medication Use

Table 2 Concomitant medication use (number of subjects taken medication) in All subjects treated (AST)

	Test (N = 35)	Control (N = 35)	*P*-value (Fisher's exact test)
Concomitant medication [N (%)]			
Overall			
Any concomitant medication	25 (71.4%)	29 (82.9%)	0.394
Subcategory*			
Dermatologicals	6 (17.1%)	16 (45.7%)	0.019
Antibiotics and chemotherapeutics	1 (2.9%)	2 (5.7%)	1.00
Antifungals	0 (0%)	5 (14.3%)	0.054
Antipruritics[a]	0 (0%)	2 (5.7%)	0.493
Antiseptics and disinfectants	1 (2.9%)	4 (11.4%)	0.356
Corticosteroids, dermatological preparations	6 (17.1%)	9 (25.7%)	0.561
Emollients and protectives	2 (5.7%)	10 (28.6%)	0.023

- Reduced use of antibiotics in children on synbiotic amino acid-based formula (AAF):
  - Particularly amoxicillin – p = 0.004

Fox et al. Clin Transl Allergy (2019) 9:5.
Burks, et al. Pediatr Allergy Immunol. 2015;26:316-22.

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Health Economic Impact of Infections in Children with CMA

- Children with CMA were estimated to generate £1559.27 per person-year in CMA-associated healthcare costs
- Children without CMA were estimated to generate £177.74 per person-year

	CMA	Non-CMA	*p*-value
Medication prescriptions			
Antibiotics			
n (%) of children[a]	3036 (87%)	2684 (77%)	<0.001
Prescription rate[b]	6.750	4.490	<0.001
Anti-reflux medications			
n (%) of children[a]	2164 (62%)	564 (16%)	<0.001
Prescription rate[b]	5.540	0.925	<0.001
Dermatological medications			
n (%) of children[a]	3002 (86%)	2460 (70%)	<0.001
Prescription rate[b]	10.105	5.185	<0.001
Inhalers			
n (%) of children[a]	1448 (41%)	1030 (29%)	<0.001
Prescription rate[b]	2.615	1.450	<0.001
Adrenaline			
n (%) of children[a]	122 (3.5%)	19 (0.5%)	<0.001
Prescription rate[b]	0.195	0.030	<0.001
None of the above prescriptions, n (%)	41 (1.2%)	314 (9.0%)	<0.001

Healthcare contacts			
GP contacts (clinic/home visit/phone)			
n (%) of children[a]	154 (4.4%)	0.150	<0.001
GP contact rate[b]	99 (2.8%)	0.100	<0.001
Dietitian contacts			
n (%) of children[a]	689 (20%)	50 (1.4%)	<0.001
Dietitian contact rate[b]	0.475	0.030	<0.001
Other specialist referrals			
n (%) of children[a]	260 (7.4%)	107 (3.1%)	<0.001
Specialist referral rate[b]	0.120	0.045	<0.001
Hospital admissions			
n (%) of children[a]	2012 (58%)	1609 (46%)	<0.001
Hospital admission rate[b]	2.220	1.460	<0.001

Cawood et al. Clin Transl Allergy. 2022;e12187.

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Conclusion

- Recent publication based on THIN database, indicates children with CMA have higher respiratory, skin and gastrointestinal infections
- This has been shown to have a significant health economic impact
- The association with increased infections have been reported by other studies, but further research is required
- Gut dysbiosis reported in studies on CMA
- Breast milk offers the best source of both pre- and probiotics and should be supported by healthcare professionals
- Manipulation of the gut microbiota through infant formula (if breast milk is not available) offers a promising option to support the immune system

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