Early Invention to reduce Allergic Risk and Enhance Gastrointestinal Intolerance

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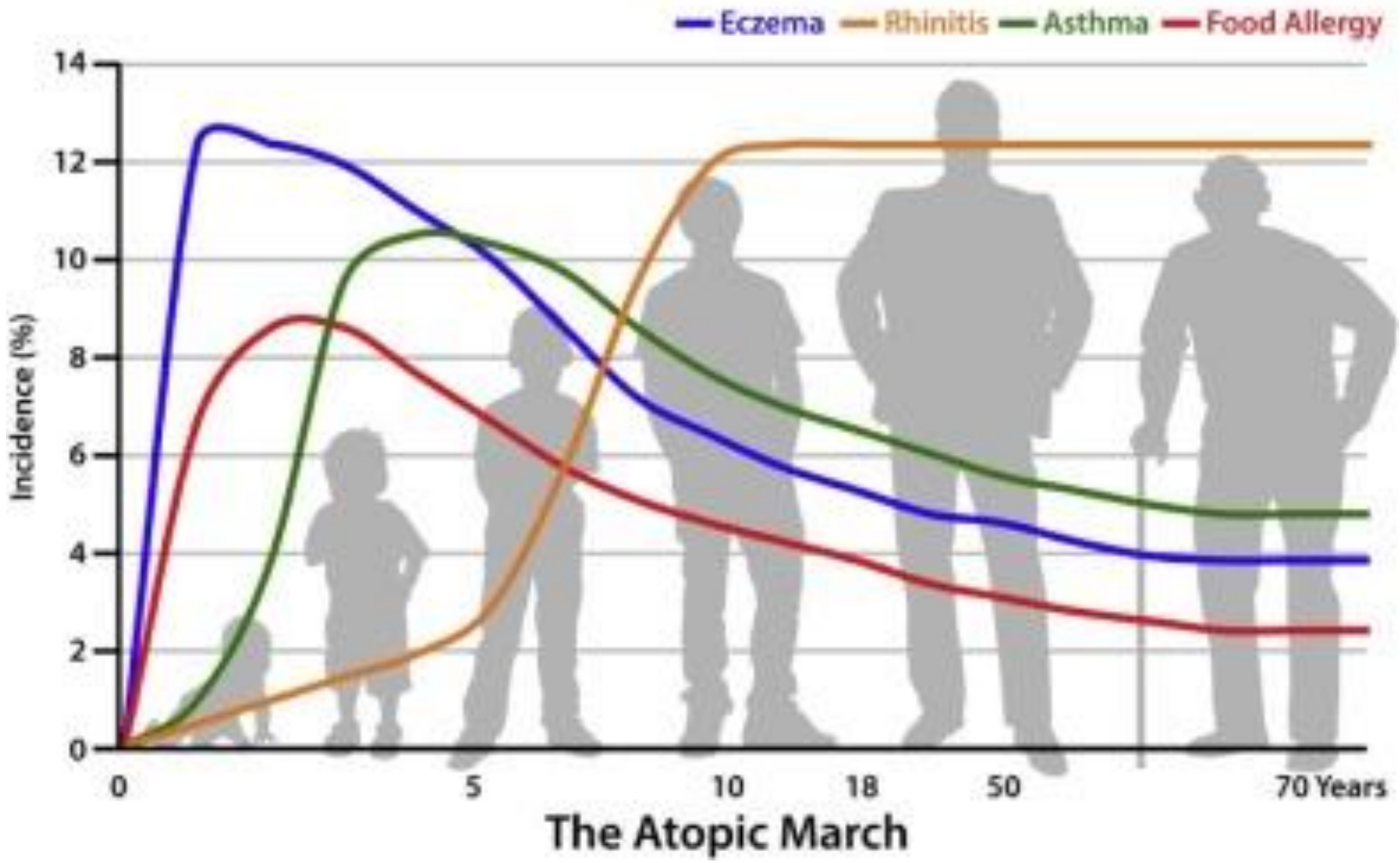
Outline

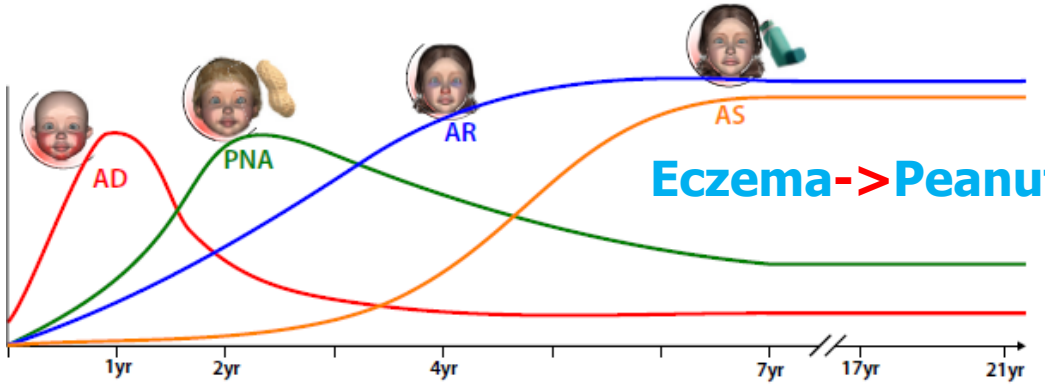
- Allergy prevention
- Gastrointestinal intolerance prevention

The Atopic March

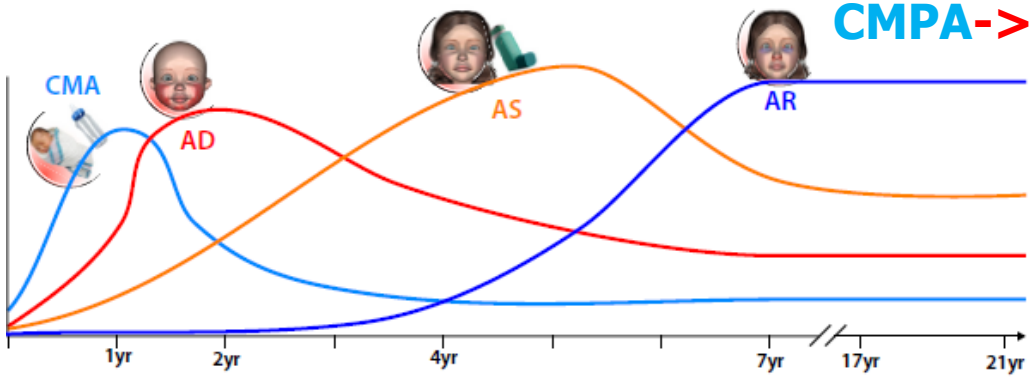


Ann Allergy Asthma Immunol 120 (2018) 115–119

Different faces of Atopic March

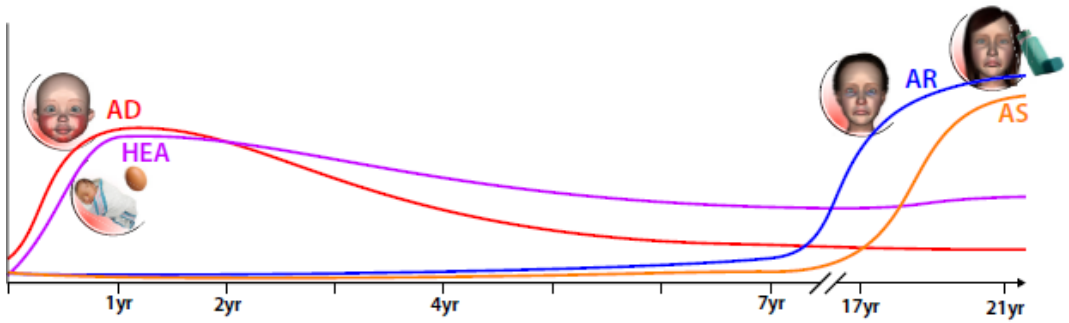


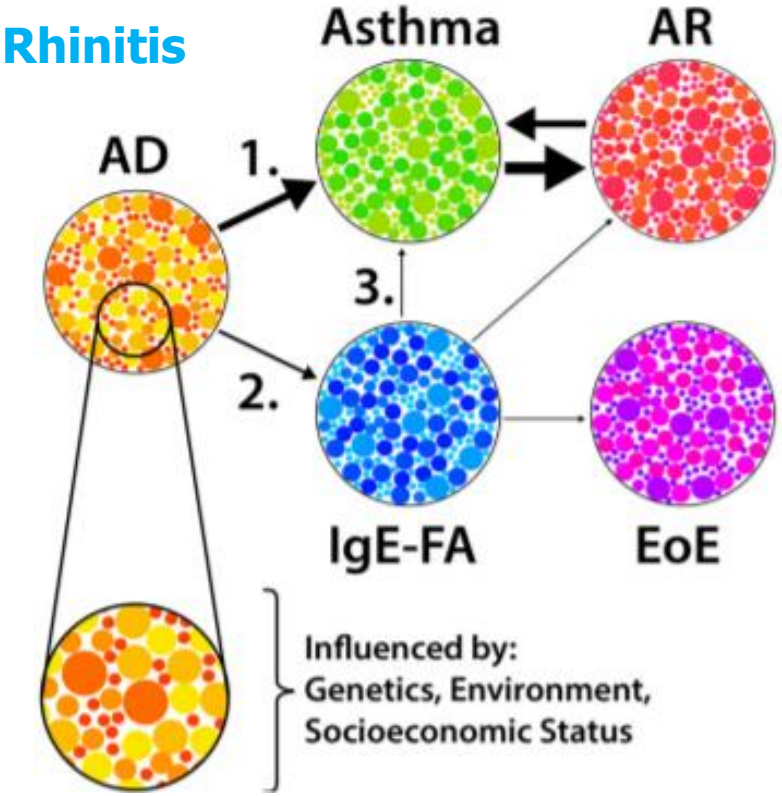
Eczema->Peanut allergy->Allergic Rhinitis->Asthma



CMPA->Eczema->Asthma->Allergic Rhinitis

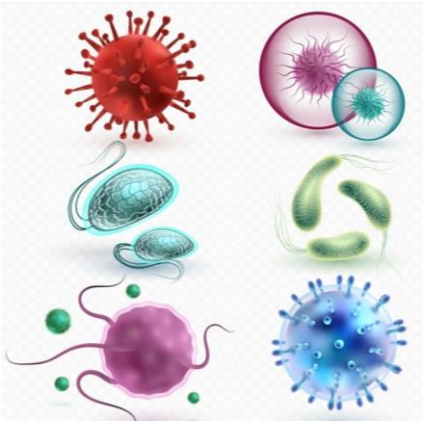
Eczema->Egg allergy->Allergic Rhinitis (late)->Asthma

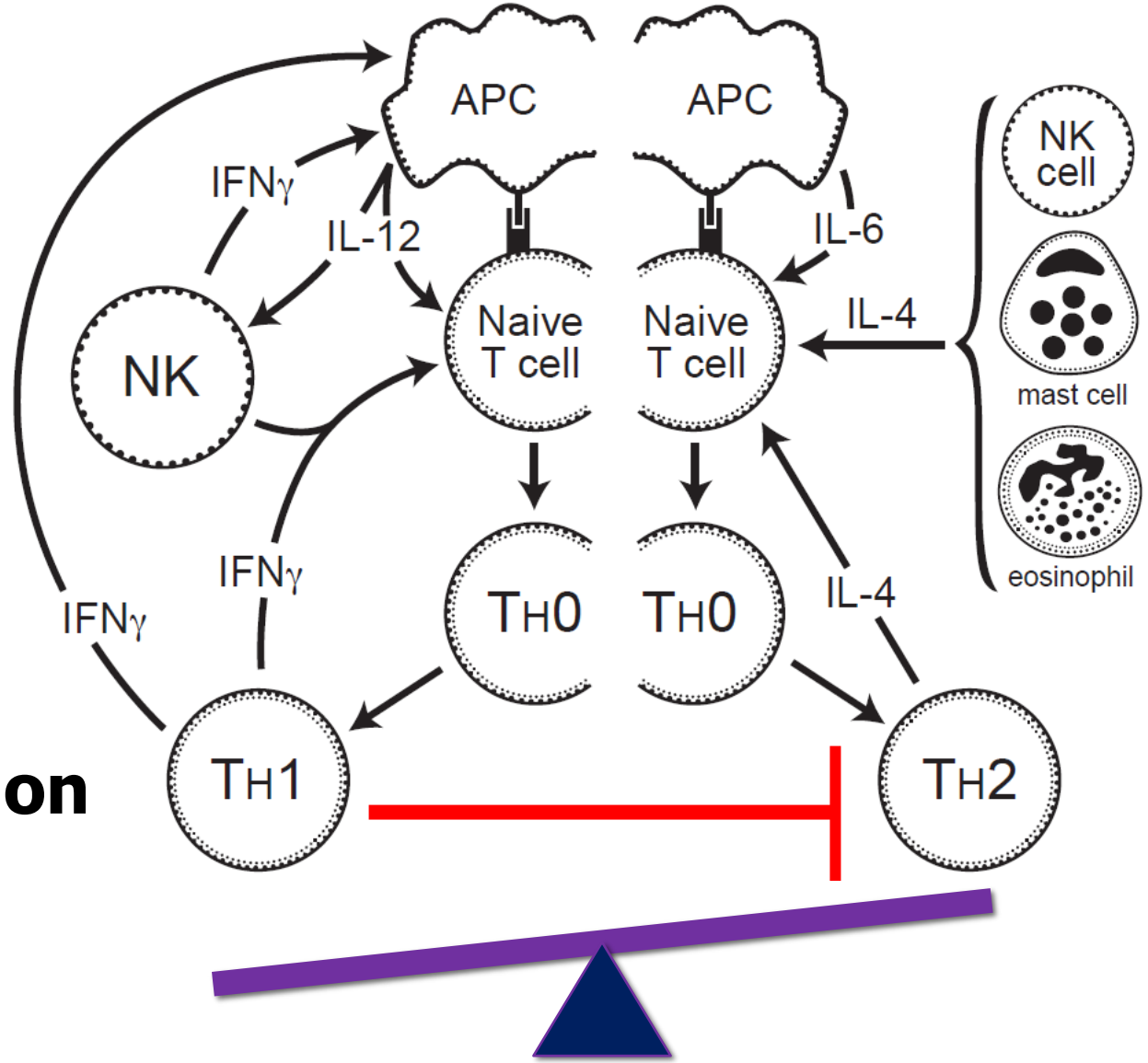


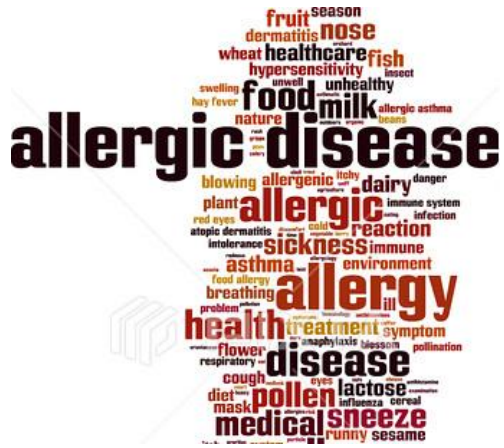


JACI prac 2020;8:860-75

Ann Allergy Asthma Immunol 127 (2021) 293–300



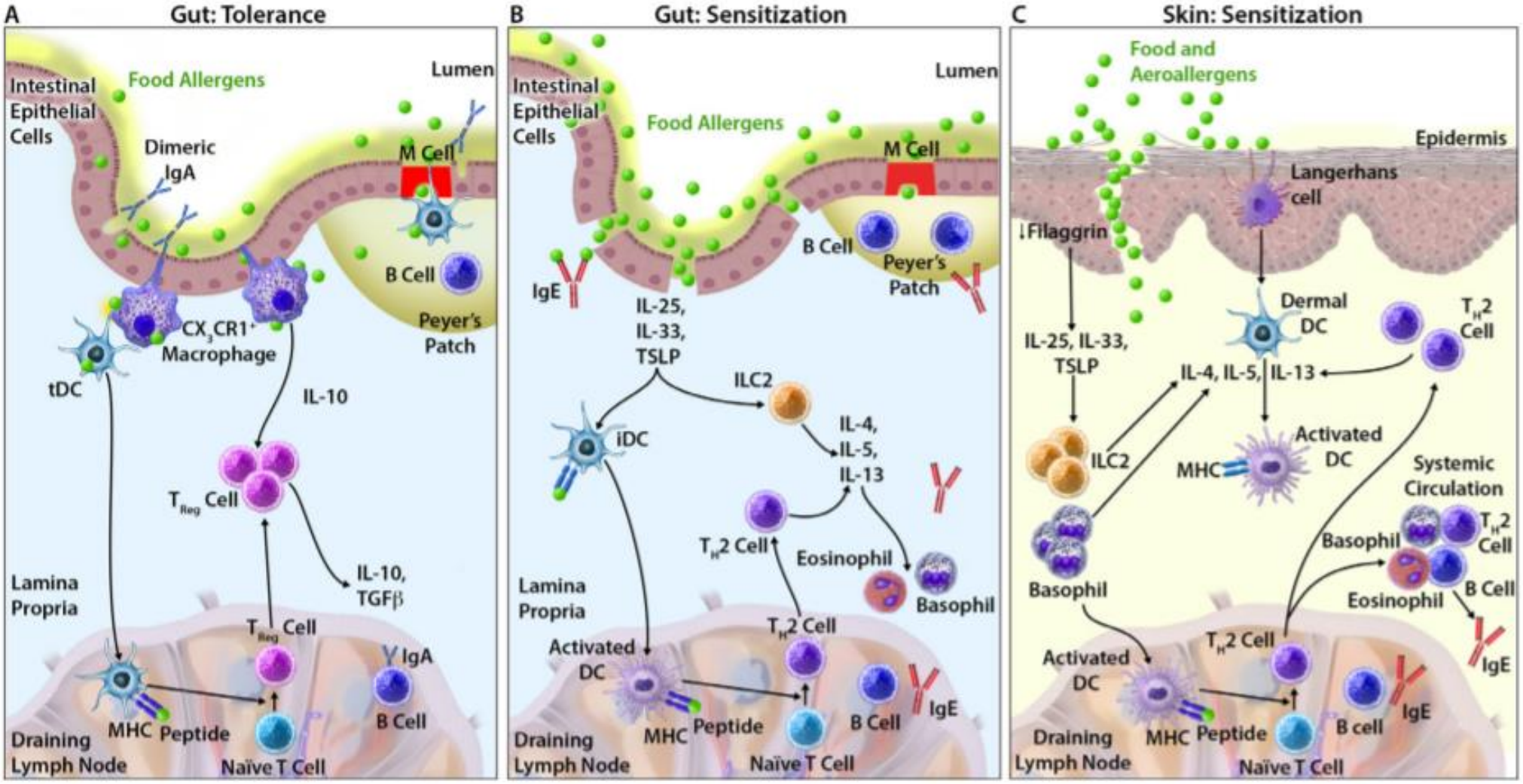




Pro-inflammation

Allergic inflammation

Mechanisms of GUT tolerance and sensitization and SKIN sensitization



Cutaneous food and aeroallergen sensitisation

Increased type 2 inflammation

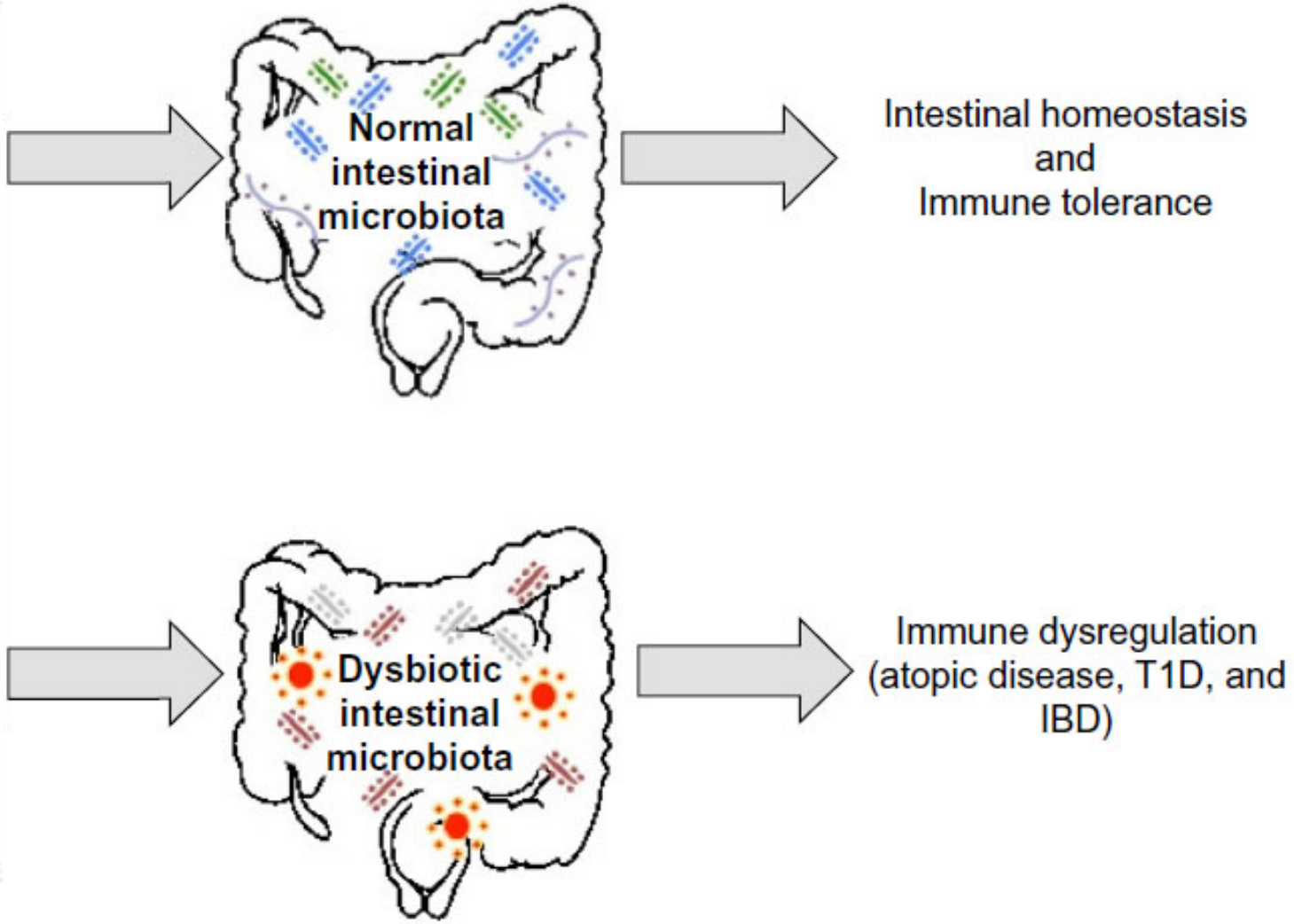
Food allergy
Atopic dermatitis
Allergic rhinitis
Atopic dermatitis

Ann Allergy Asthma Immunol 127 (2021) 293–300

The hygiene hypothesis: roles of intestinal microbiota

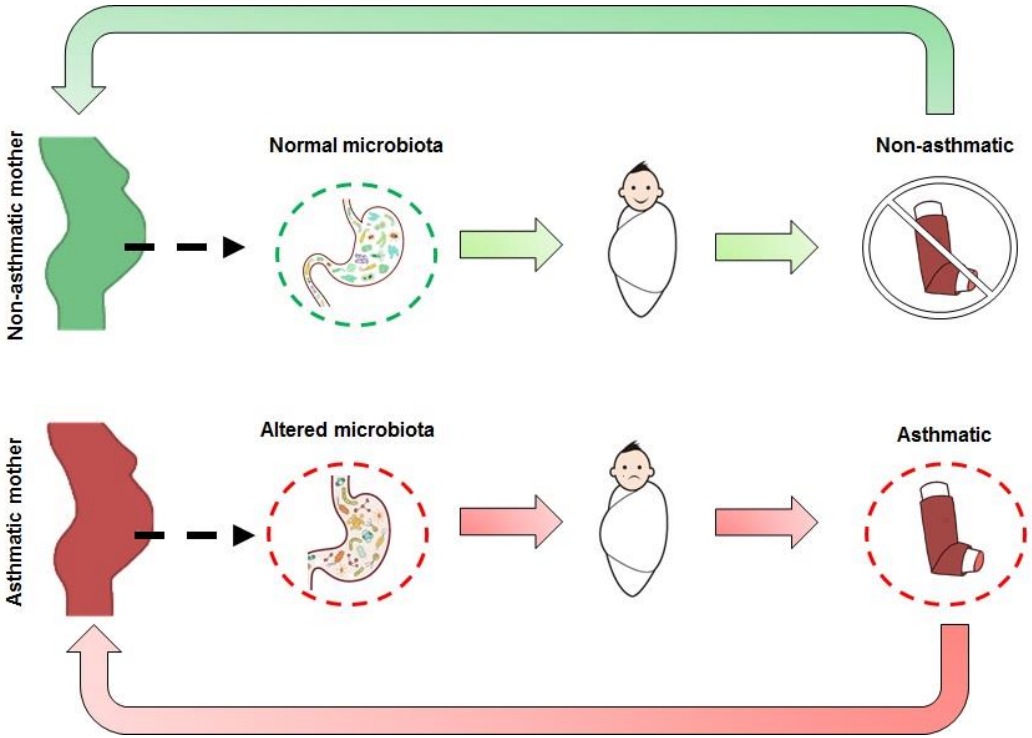
Early life exposures

- Diet (breast milk vs formula)
- Birth mode (vaginal vs Caesarean section)
- Infection
- Antibiotic exposure
- Household size and number of siblings
- Furred pet exposure



Stiemsma, Leah T et al. "ImmunoTargets and therapy vol. 4 143-57. 27 Jul. 2015, doi:10.2147/ITT.S61528

Microbiome in severe asthma



Inception

Lung development during antenatal life

Role of early events

Wheezing Illness

Atopy

Resolution

Asthma

Prevention

Infant

Viral infections

Smoking

↑ Th1 Th2 Th17

↓ Th1

↓ Allergy/ Asthma

↑ Th2 → Allergy/ Asthma

Exacerbation

Child or adult with asthma

Rhinovirus

Exacerbation of asthma

- Emergency department visits
- Hospitalization

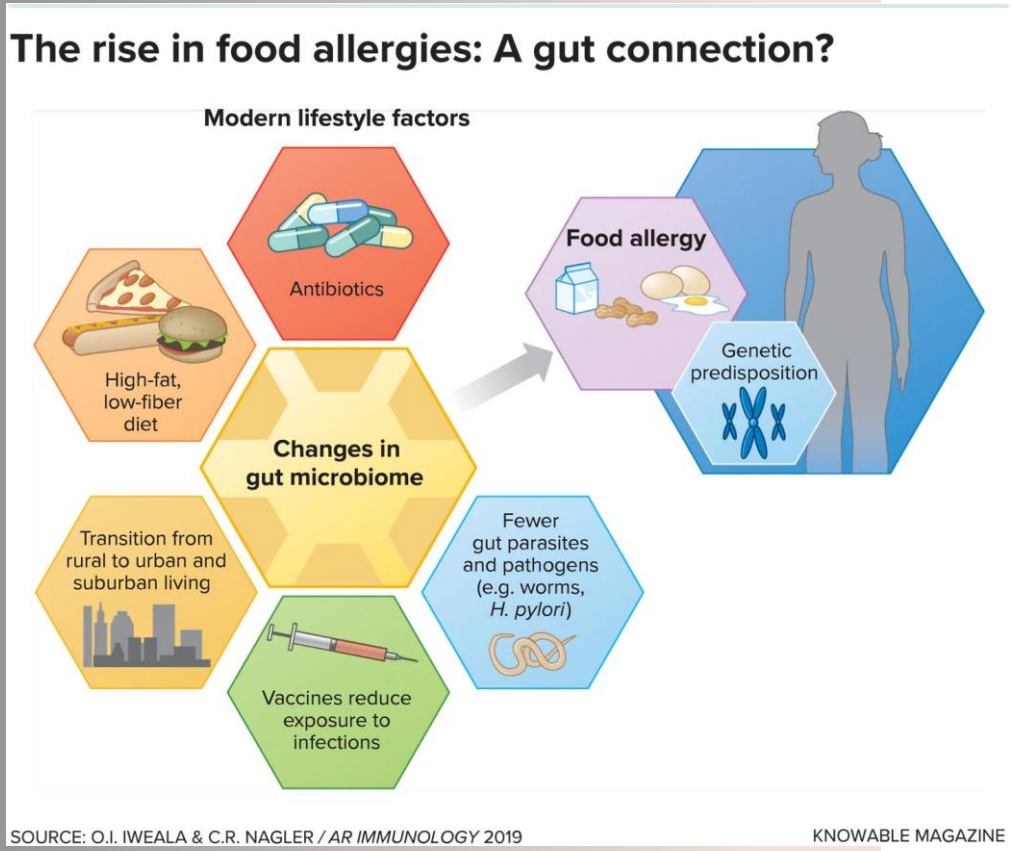
Persistence

Adult (Preexisting Asthma)

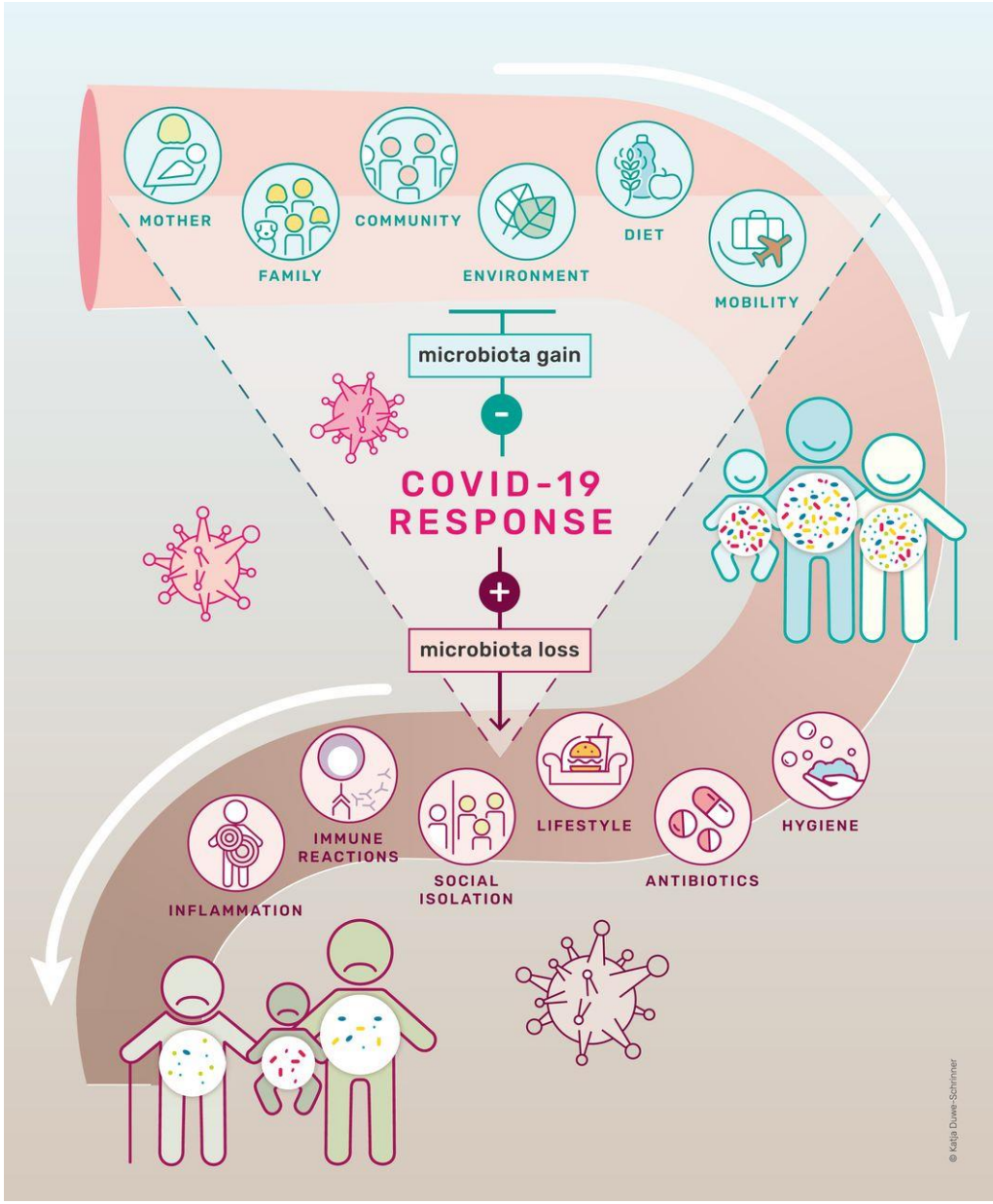
Persistent Asthma

SEVERE ASTHMA

Mezouar et al. Human Microbiome Journal. Volume 10, December 2018, Pages 11-20



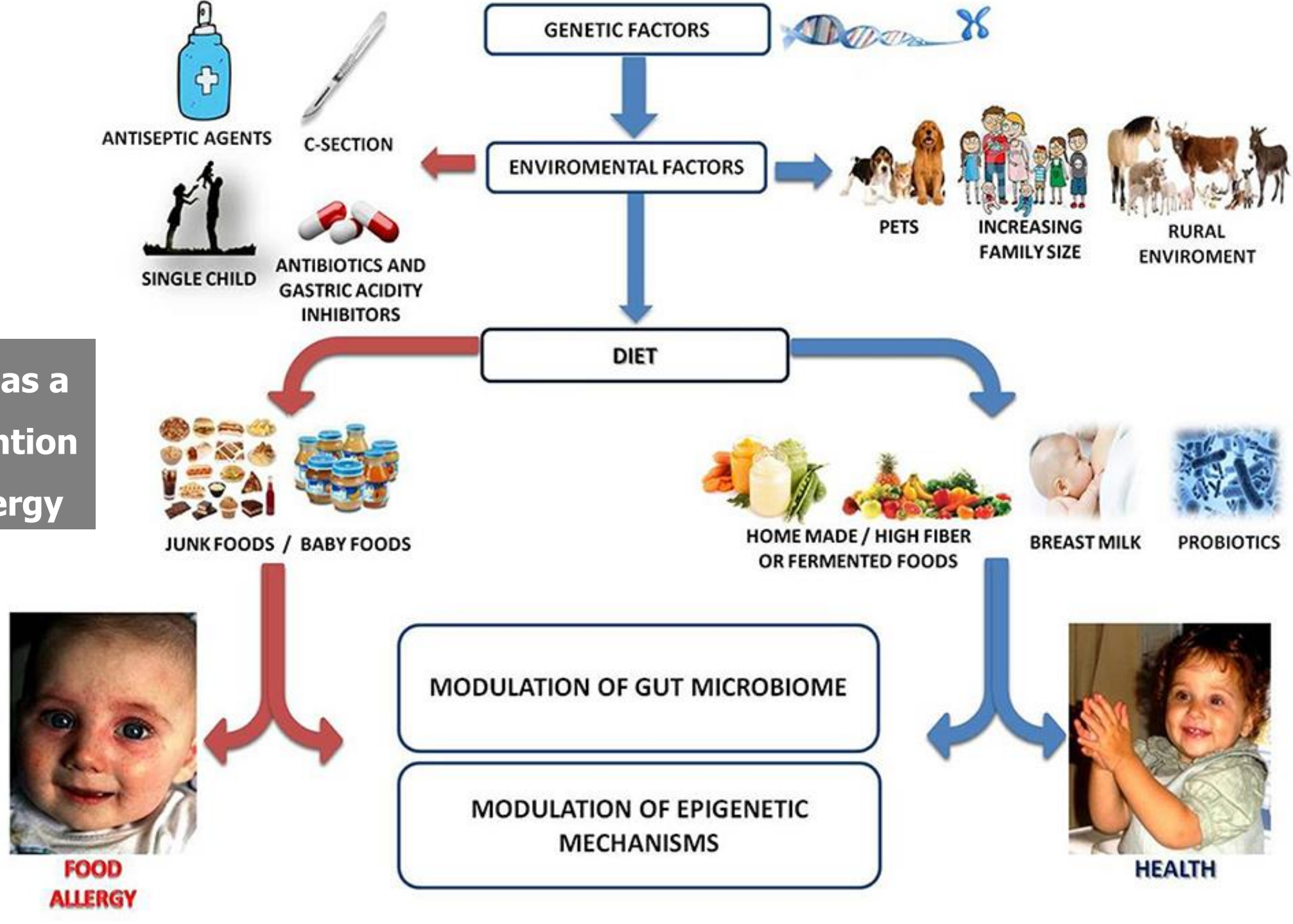
The hygiene hypothesis, the COVID pandemic, and consequences for the human microbiome

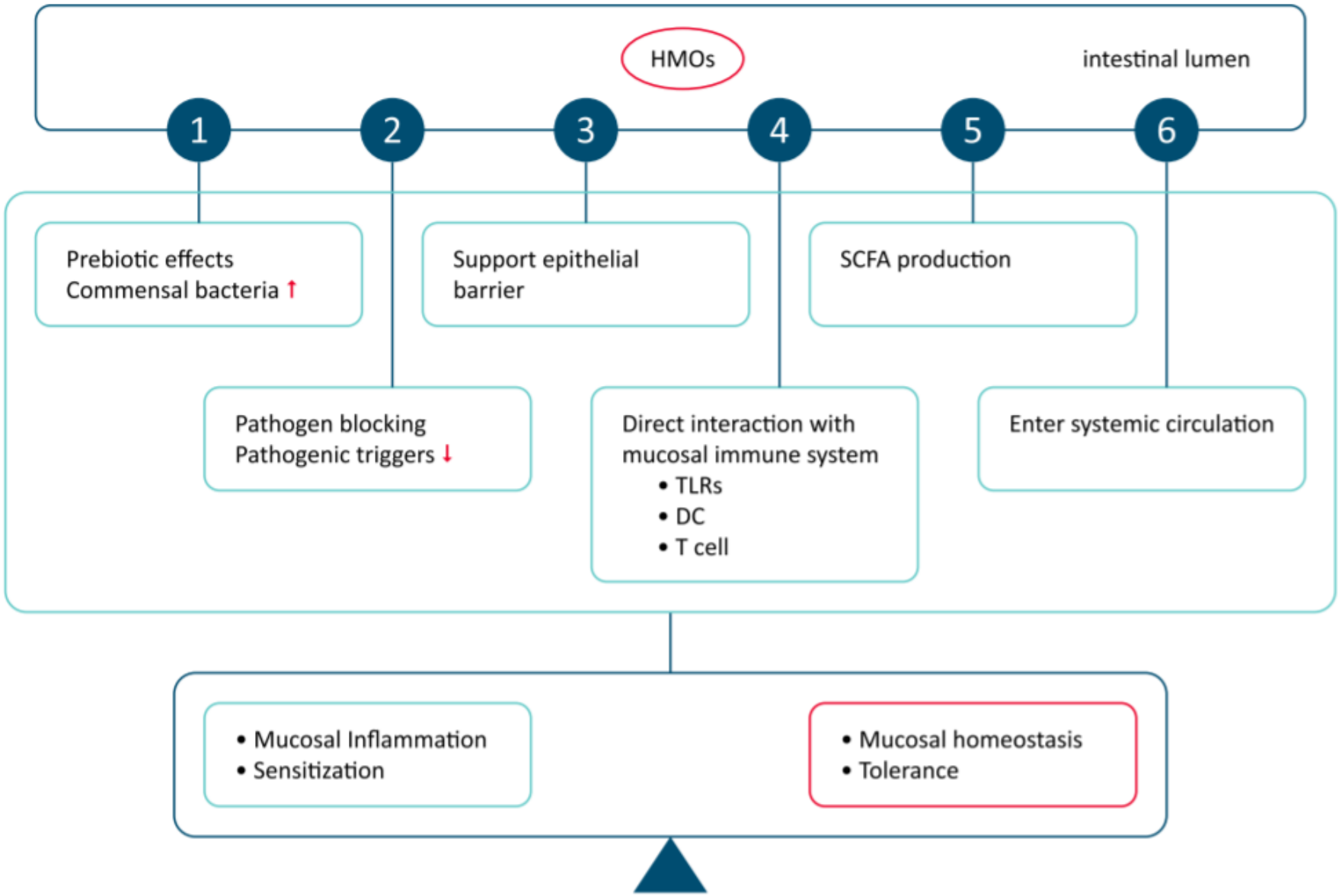


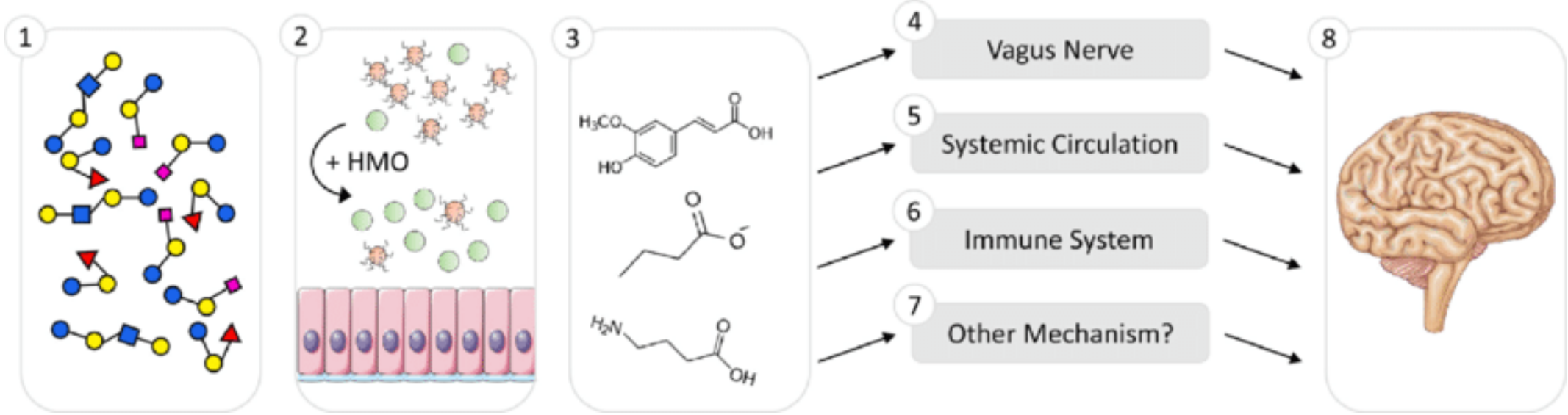
Physical separation, extensive hygiene, travel barriers, and other measures that influence overall microbial loss and inability for reinoculation

B. Brett Finlay et al. Proceedings of the National Academy of Sciences Feb 2021, 118 (6) e201021711

Gut microbiome as a target of intervention against food allergy




HMOs
intestinal lumen
1
2
3
4
5
6
Prebiotic effects
Commensal bacteria ↑
Support epithelial barrier
SCFA production
Pathogen blocking
Pathogenic triggers ↓
Direct interaction with mucosal immune system
• TLRs
• DC
• T cell
Enter systemic circulation
• Mucosal Inflammation
• Sensitization
• Mucosal homeostasis
• Tolerance

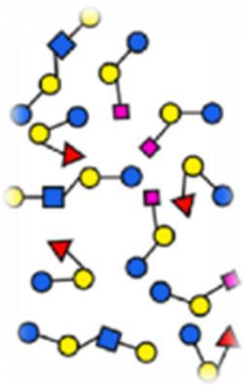


- specific gut bacteria can utilize HMO
- Most strains of B. longum subsp. infantis and B. bifidum

HMOs have shown to

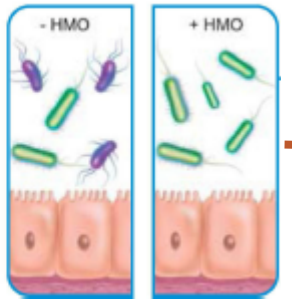
- inhibit binding and colonization of certain pathogens in the intestine in vitro
- interact with the epithelial wall and affect cells of the immune system

Biologic roles of human milk oligosaccharides



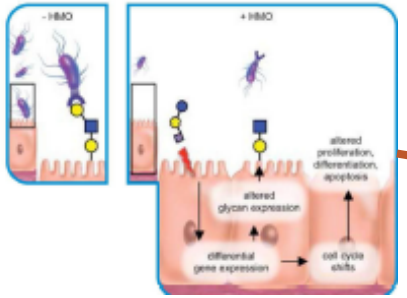
Promote healthy microbiota composition

Prebiotics



Maturation of intestinal mucosa and intestinal epithelial barrier function

Intestinal epithelial cell modulation



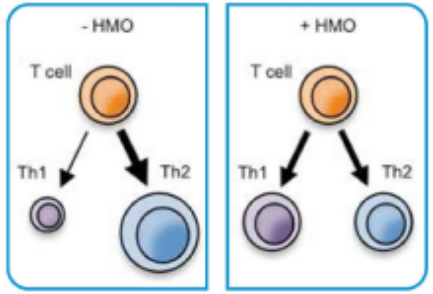
Affect immune cells on a systemic level

Modulation of immune cells and pathogen recognition receptors

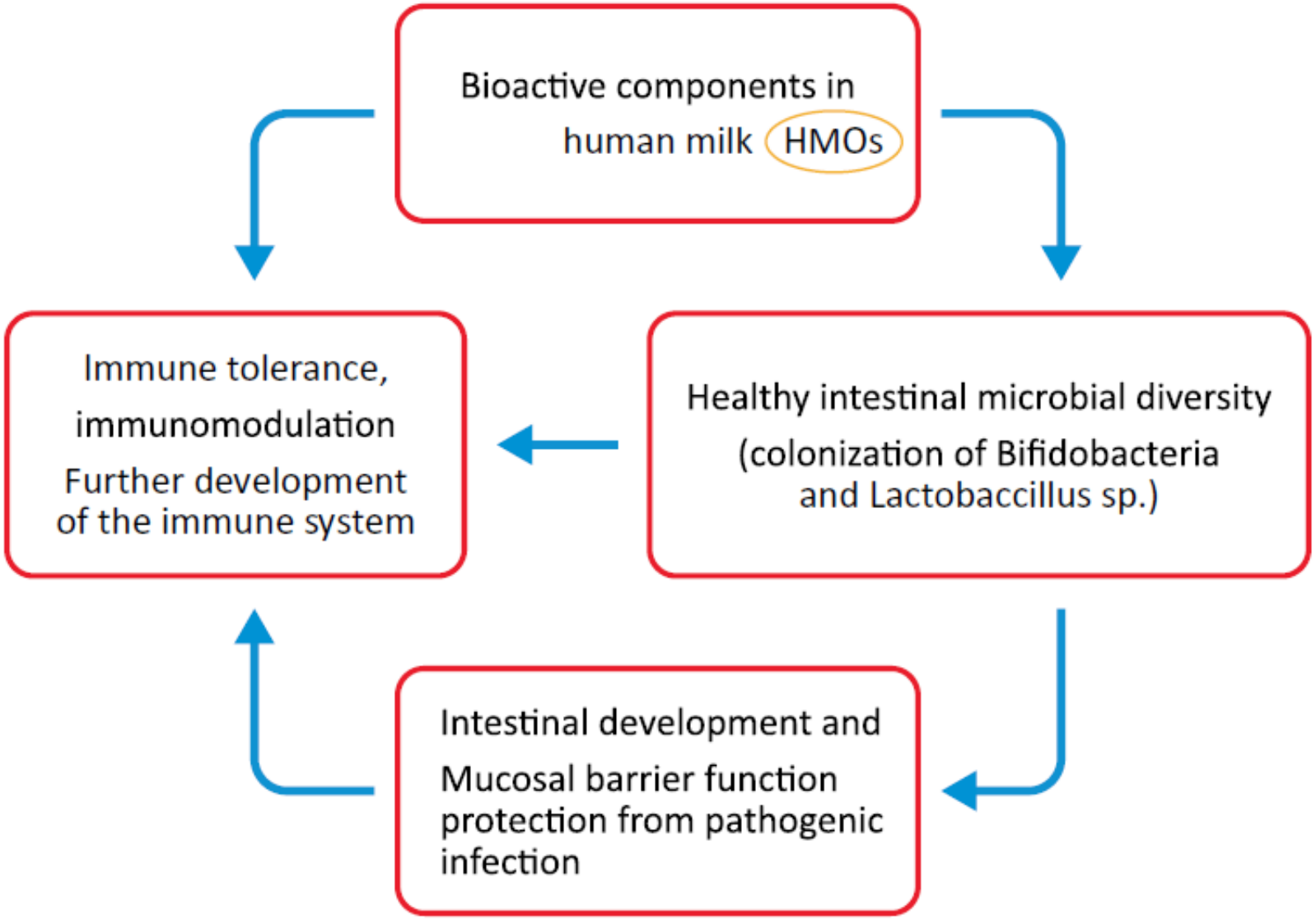
Modulation of signaling pathways related to maturation of lymphoid tissue, cytokine and chemokine networks that regulate Th1/Th2 lymphocyte balance

Prevention of infection and support of immunity

Immunomodulation
Immune maturation

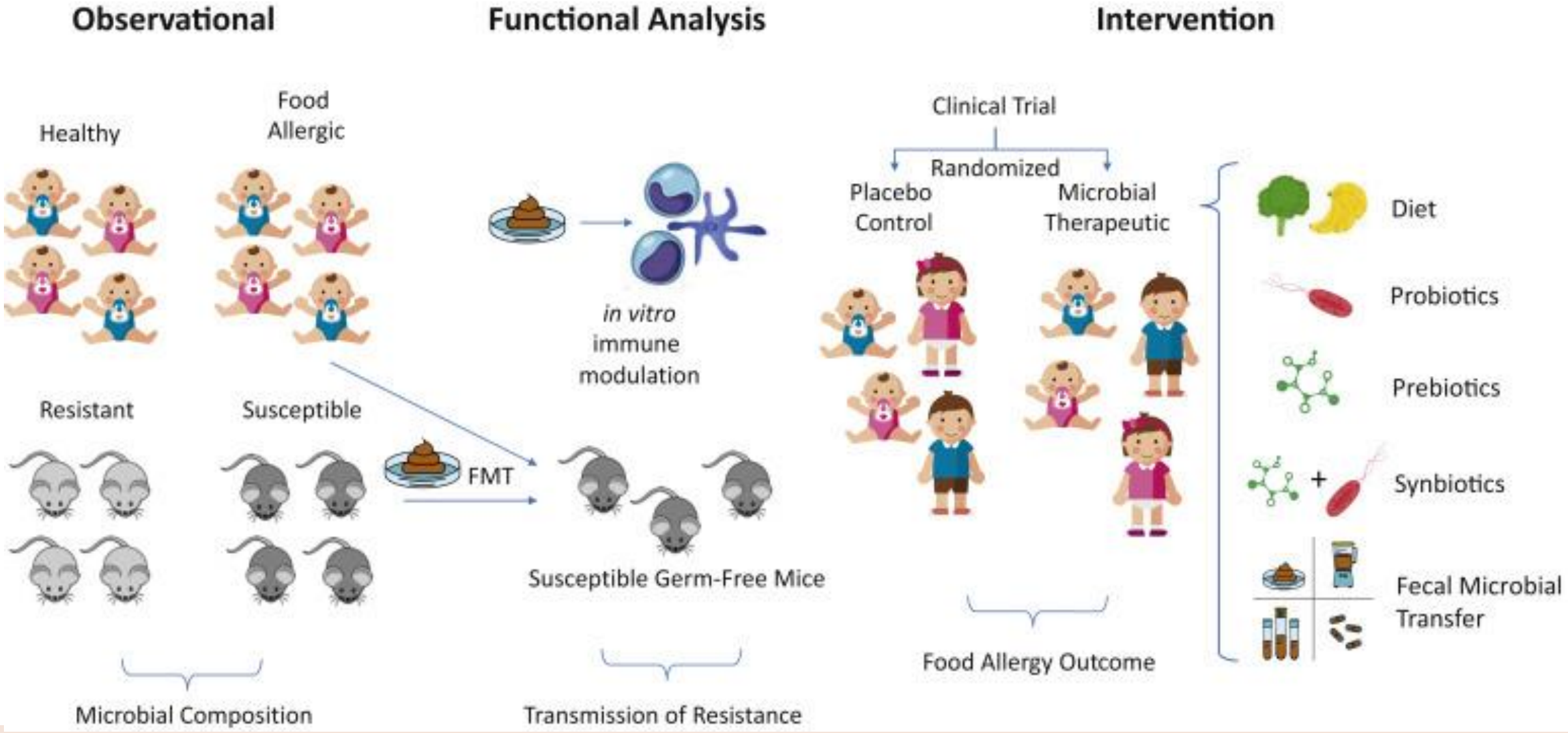


Human milk bioactive components and immunomodulation pathways



Journal of Asthma and Allergy 2021:14 1147–1164

Pathways to the development of microbial therapeutics for food allergy



Bunyavanich S. J Allergy Clin Immunol. 2019 Dec;144(6):1468-1477.

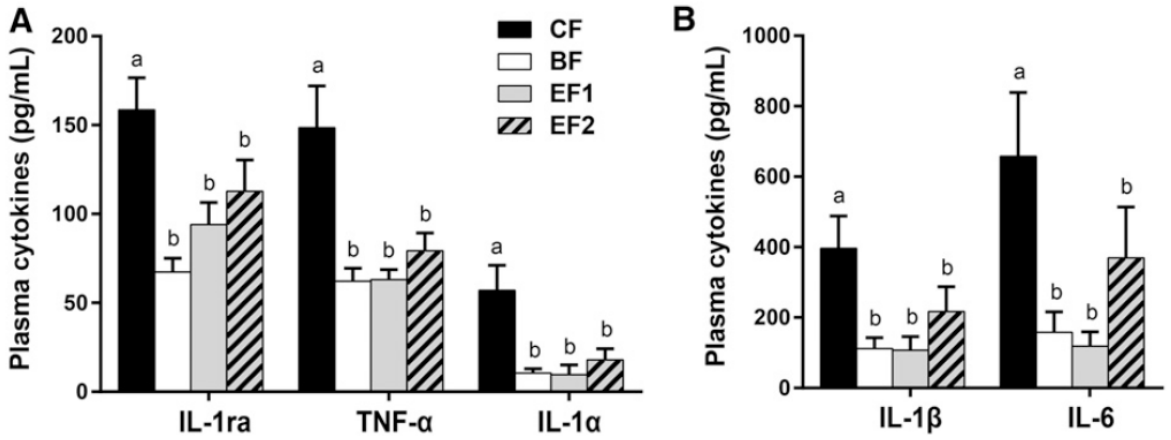
Composition of study formulas

Ingredient	CF	EF1	EF2
Energy, kcal/dL	64.3	64.3	64.3
Protein, g/L	13.3	13.3	13.3
Fat, g/L	34.7	34.7	34.7
Total carbohydrate, g/L	69.0	69.0	69.0
GOS, g/L	2.4	2.2	1.4
2′-FL, g/L	—	0.2	1.0

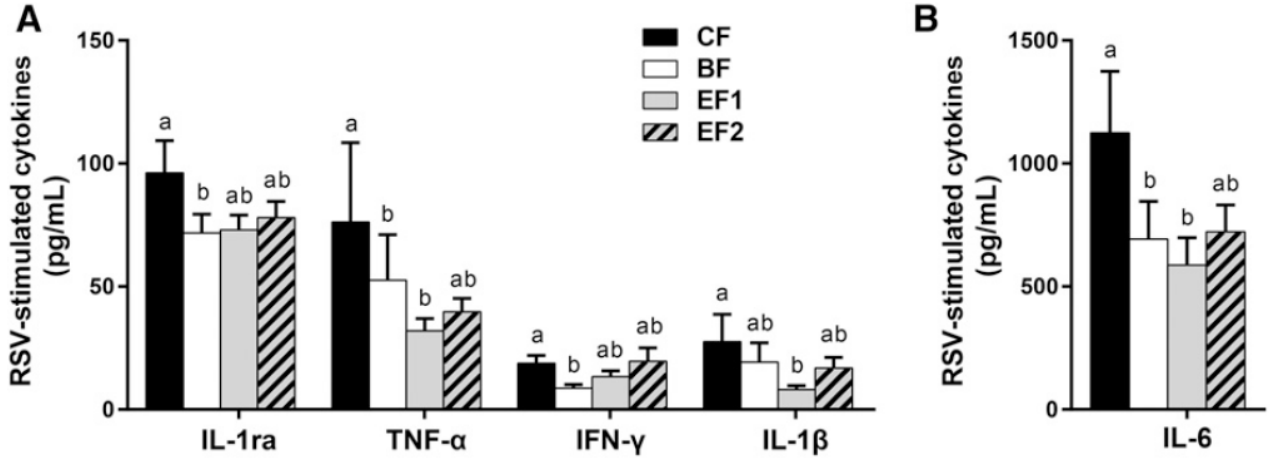
Lower Inflammatory Cytokines in 2'FL formula fed similar to BF

	CF (n = 48)	BF (n = 51)	EF1 (n = 54)	EF2 (n = 48)	P^2
Age at enrollment, d	3.8 ± 0.1	3.5 ± 0.2	3.4 ± 0.2	3.8 ± 0.2	0.30
Males, n (%)	27 (56)	31 (61)	24 (44)	23 (48)	0.32
Gestational age, wk	39.3 ± 0.2	39.4 ± 0.1	39.2 ± 0.1	39.4 ± 0.2	0.51
Birth weight, g					
Males	3338 ± 70	3498 ± 92	3248 ± 75	3322 ± 86	0.17
Females	3269 ± 94	3354 ± 78	3188 ± 83	3191 ± 69	0.27
Mode of delivery, n (%)					0.58
Vaginal	30 (63)	38 (75)	38 (70)	35 (73)	
Cesarean	18 (38)	13 (25)	16 (30)	13 (27)	
Number of siblings in home, n	1.3 ± 0.2	1.2 ± 0.2	1.5 ± 0.2	1.2 ± 0.2	0.55

Plasma cytokine concentrations in 6-wk-old infants who were exclusively breastfed or fed GOS-containing CF alone or with 0.2 or 1.0 g 2#-FL/L from 5 d until 4 mo of age



Ex vivo cytokine production by RSV-stimulated PBMCs



Goehring et al. J Nutr 2016;146:2559–66.

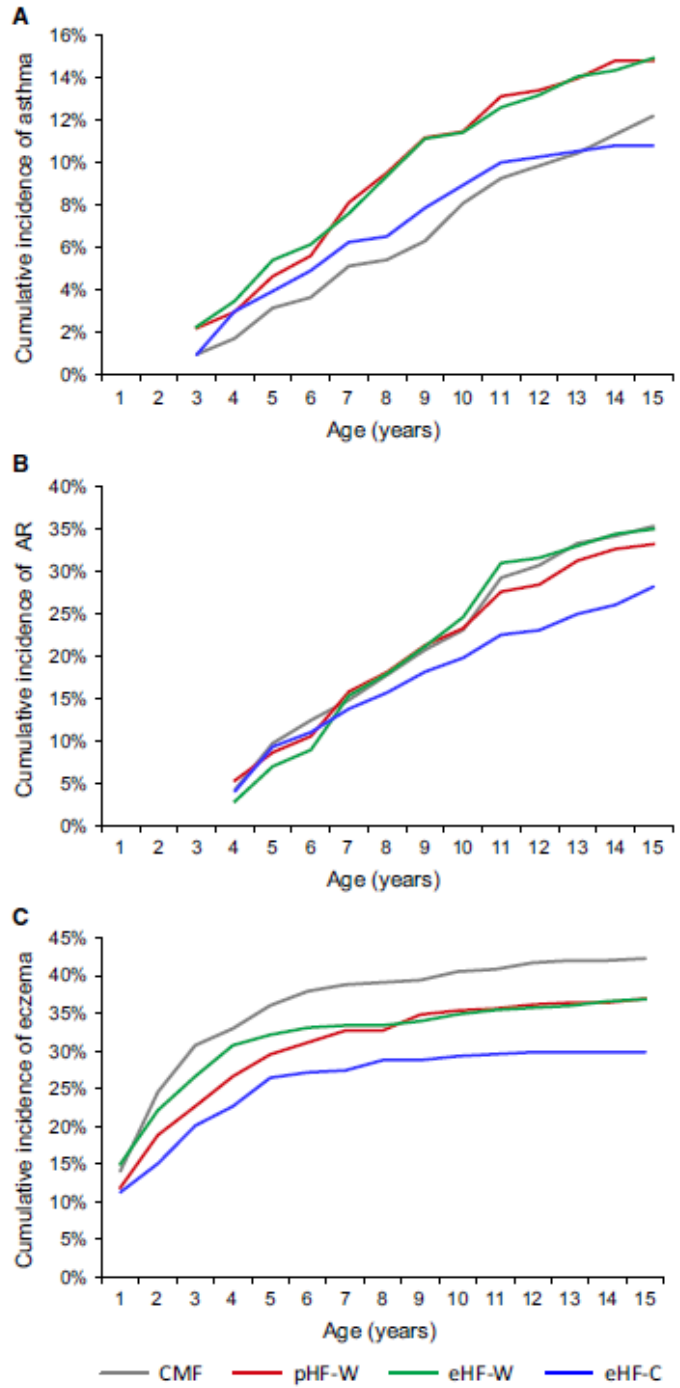
Allergic manifestation after early intervention with hydrolyzed formulas from year 1 to year 15

Von Berg JACI 2003;111:533-40
Von Berg Allergy 71 (2016) 210–219

	CMF	pHF-W	eHF-W	eHF-C
No. of patients	256	241	238	210
AD				
n	38	22	31	15
%	14.8	9.1	13.0	7.1
Urticaria				
n	1	0	1	3
%	0.4	0.0	0.4	1.4
FA-GIT				
n	1	5	2	4
%	0.4	2.1	0.8	1.9
AM				
n	40	26	34	19
%	15.6	10.8	14.3	9.1
Crude OR	1	0.65	0.90	0.54
95% CI		(0.39-1.1)	(0.55-1.5)	(0.30-0.96)
P value		.114	.677	.036

TABLE III. Incidence of AM in groups of potential risk factors and crude ORs by simple logistic regression models

	n/N* (%)	OR (95% CI)	*P* value
Sex			
Female	44/446 (10)	1	
Male	75/499 (15)	1.6 (1.1-2.4)	.018
FH of allergy			
Single	76/667 (11)	1	
Double	43/278 (16)	1.4 (0.95-2.1)	.087
AD in FH			
No	57/596 (10)	1	
Yes	62/342 (18)	2.1 (1.4-3.1)	<.001
Parental education			
<10 y	13/95 (14)	1.0 (0.51-1.9)	.665
10 y	43/313 (14)	1	
≥12 y	63/536 (12)	0.84 (0.55-1.3)	.399
Parental nationality			
German	103/814 (13)	1	
Non-German	15/128 (12)	0.92 (0.52-1.6)	.767
Siblings			
No	70/569 (12)	1	
Yes	48/369 (13)	1.1 (0.72-1.6)	.750
Study center			
North Rhine Westphalia	64/503 (13)	1	
Bavaria	55/442 (12)	0.98 (0.66-1.4)	.897



Gastrointestinal intolerance prevention

- 50% of infants suffer from functional gastrointestinal disorders
- 75% of these infants present with more than one symptom

F1000Res. 2018 Sep 7;7:F1000 Faculty Rev-1426.

Conditions to Consider in the Evaluation of Unexplained Crying in Infants

Findings	*Possible cause*	*Other historical clues*	*Physical examination findings*	*Diagnostic testing*
Vomiting, recurrent and/or forceful	Gastroesophageal reflux disease	Apnea, arching of the back with feeding, cough, feeding refusal, hematemesis, irritability, poor weight gain, wheezing	Nonspecific	None required in uncomplicated reflux; 24-hour pH monitoring may be used for complicated reflux; endoscopy for persistent symptoms
	Pyloric stenosis	Normal appetite, progressive nonbilious projectile vomiting; more common in boys; presents at two to six weeks of age	Clinical dehydration, palpable pyloric mass or "olive" in right midepigastrium, visualization of gastric peristalsis with feeding	Ultrasonography of pylorus
No clinical signs or symptoms	Anal fissure	Bloody or painful bowel movements	Fissure	None
	Corneal abrasion	Tearing	Conjunctival erythema, scratches near the eye	Fluorescein testing
	Cow's milk allergy	Bloody stools, constipation, diarrhea, excessive gas, pain with defecation, rash, vomiting	Rash	Fecal occult blood testing, resolution of symptoms after maternal dietary change (in breastfed infants) or formula change
	Hair tourniquet syndrome	Edema of toes, fingers, or penis; hair found curled up near infant	Hair wrapped around finger, toe, or penis	None
	Inadequate bottle feeding	Aggressive feeding	Clinical dehydration, loss of fat from cheeks, weight loss or poor weight gain	Weight increase with increase in formula feedings
	Inadequate breastfeeding	Breasts not emptying with feeding	Poor latch observed; weight loss or poor weight gain	Weight increase with supplemental formula

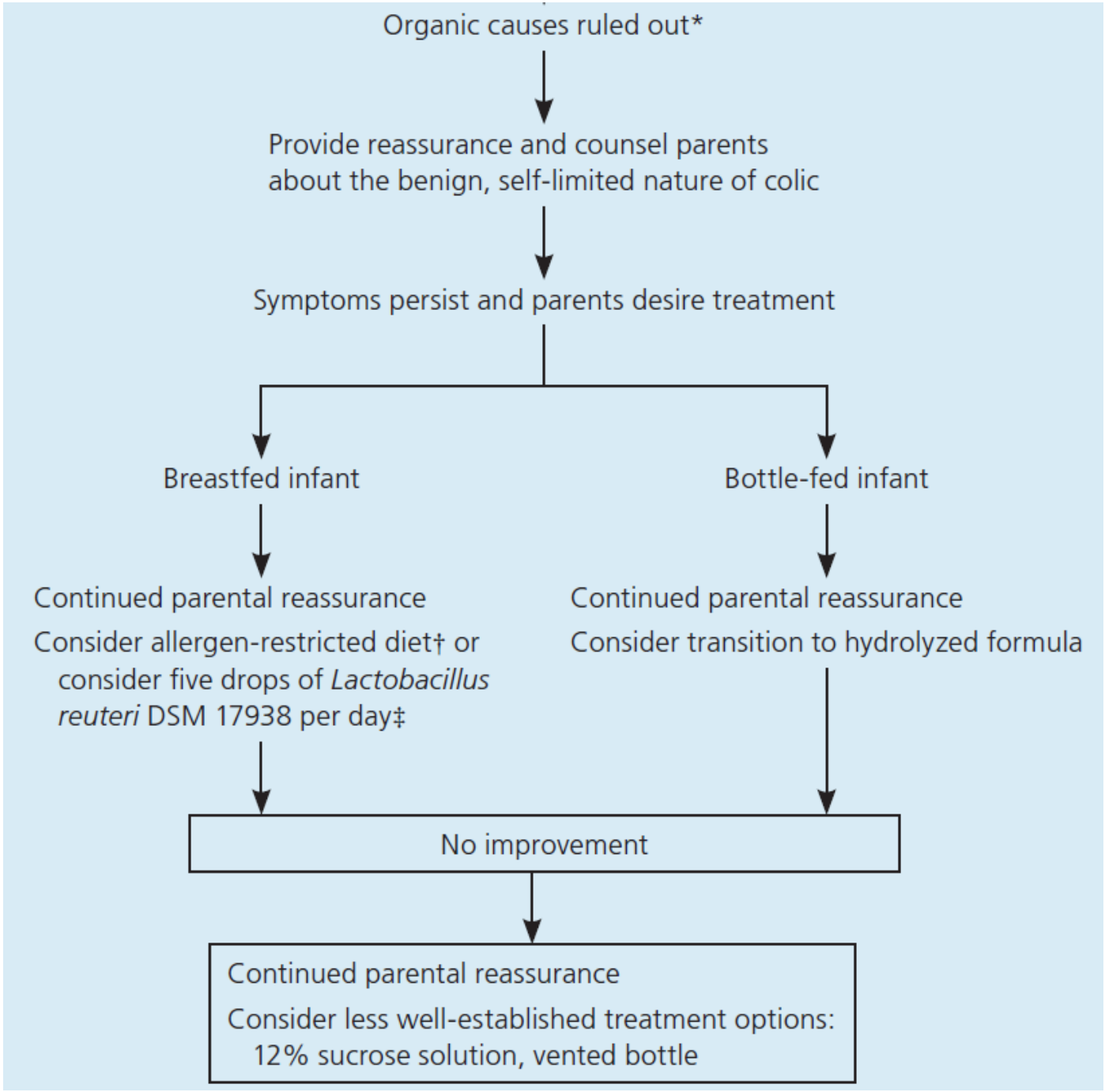
Am Fam Physician. 2015 Oct 1;92(7):577-582.

Conditions to Consider in the Evaluation of Unexplained Crying in Infants

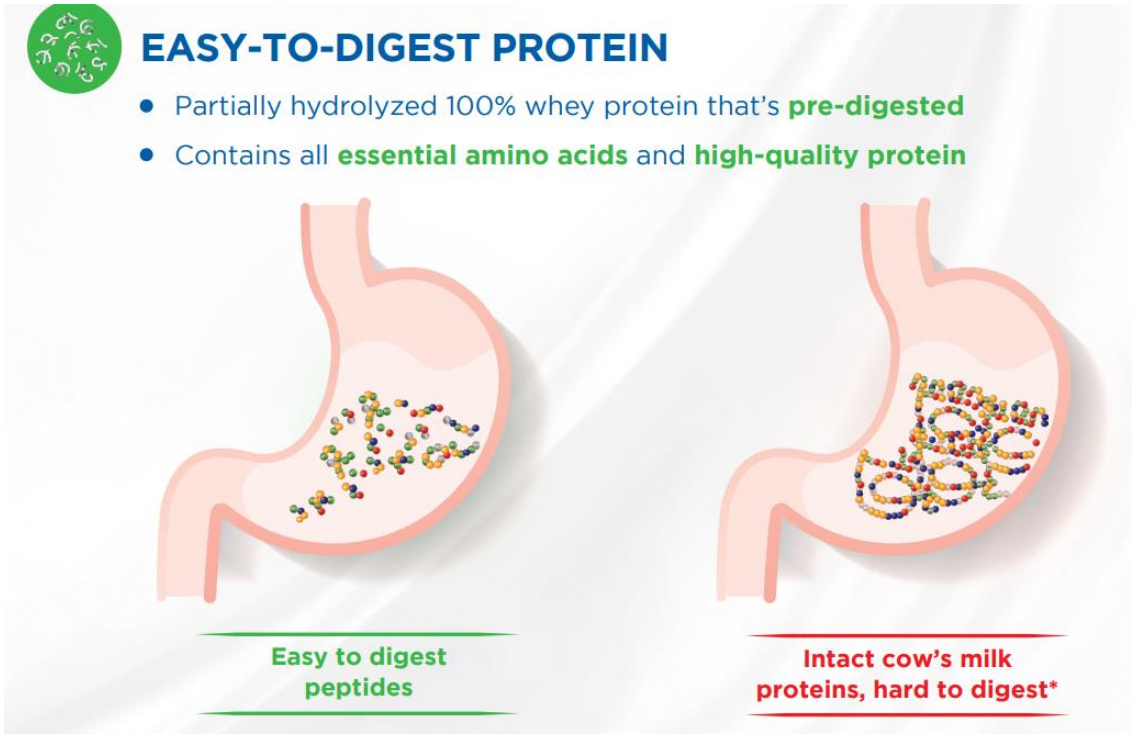
Findings	*Possible cause*	*Other historical clues*	*Physical examination findings*	*Diagnostic testing*
Diarrhea, intermittent, explosive	Hirschsprung disease	Bilious emesis, chronic constipation, fever, no meconium passed in first 24 hours of life, poor feeding; may coexist with trisomy 21; more common in boys	Abdominal distention or tenderness, jaundice	Abdominal radiography (with or without contrast enema), anorectal manometry, rectal suction biopsy
Scrotal or inguinal swelling	Incarcerated hernia	Abdominal pain, bilious emesis	Abdominal bulging or distention, acute abdomen	Ultrasonography
	Testicular torsion	Acute onset of crying and pain	High-riding testicle, scrotal discoloration, tenderness to palpation	Ultrasonography
Tenderness to palpation in long bones, clavicles, or scalp	Child abuse	History of fall or trauma, lethargy, unwillingness to move extremities	Burns, frenulum tears, geographic scars, retinal hemorrhage, suspicious bruises	Computed tomography to detect intracranial hemorrhage, radiography of extremities

Am Fam Physician. 2015 Oct 1;92(7):577-582.

Treatment of Colic in Infants



Am Fam Physician. 2015 Oct 1;92(7):577-582.



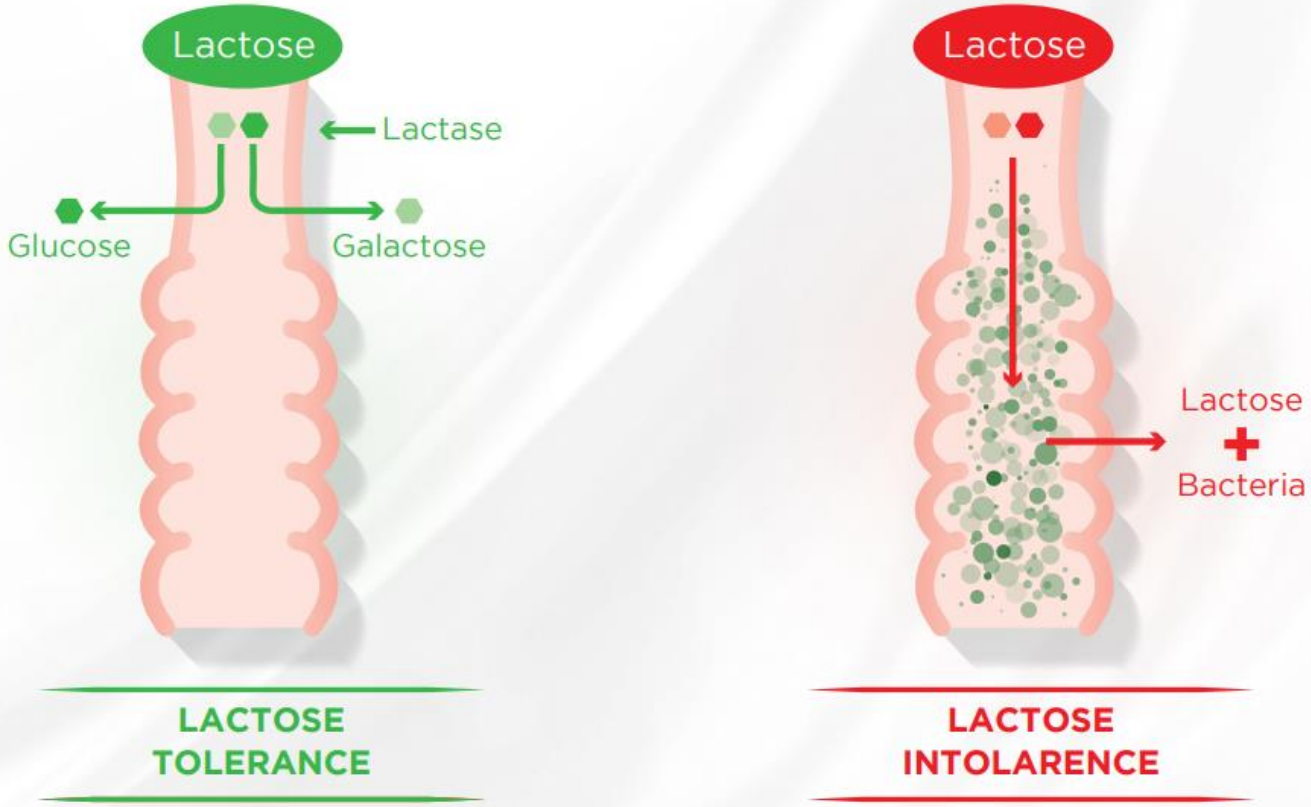
Systematic review of the impact of feed protein type and degree of hydrolysis on gastric emptying in children

Rosan Meyer[1*], Ru-Xin Melanie Foong[1], Nikhil Thapar[2,1], Stamatiki Kritas[3] and Neil Shah[1,2]

1. Breast milk empties the stomach faster than whole protein infant formula.
2. Predominant whole casein feeds empty slower when compared to predominant whey feeds in children with CP and GOR.
3. Differences in GE data exists between healthy children and those with underlying conditions.
4. Whole versus hydrolysed protein may affect children differently depending on their underlying diagnosis and age.

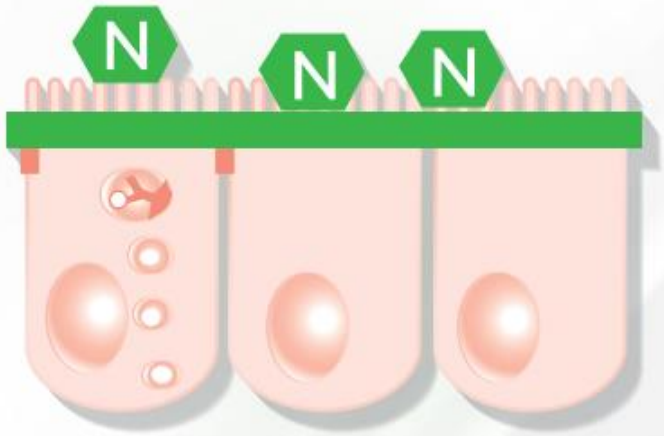
Meyer et al. BMC Gastroenterology (2015) 15:137

2% LACTOSE TO AVOID SENSITIVITY



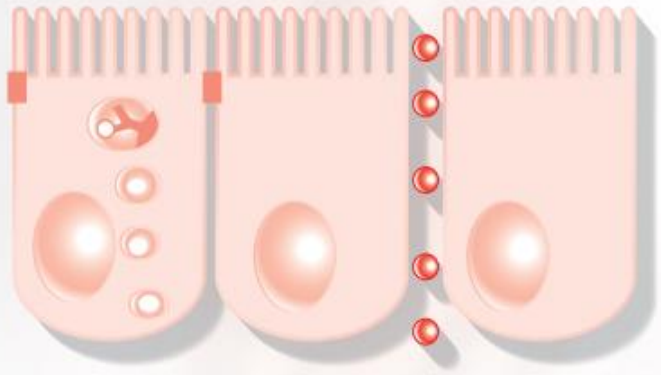
NUCLEOTIDES ARE IMPORTANT FOR GUT HEALTH

- Nucleotides is building block of DNA
- Gut epithelial cells are important for immunity. It replenishes within only 2-3 days, constant supply of nucleotides is required



Nucleotides are important to maintain good gut health and epithelial barrier integrity

Sufficient Nucleotides



Can lead to Leaky gut*

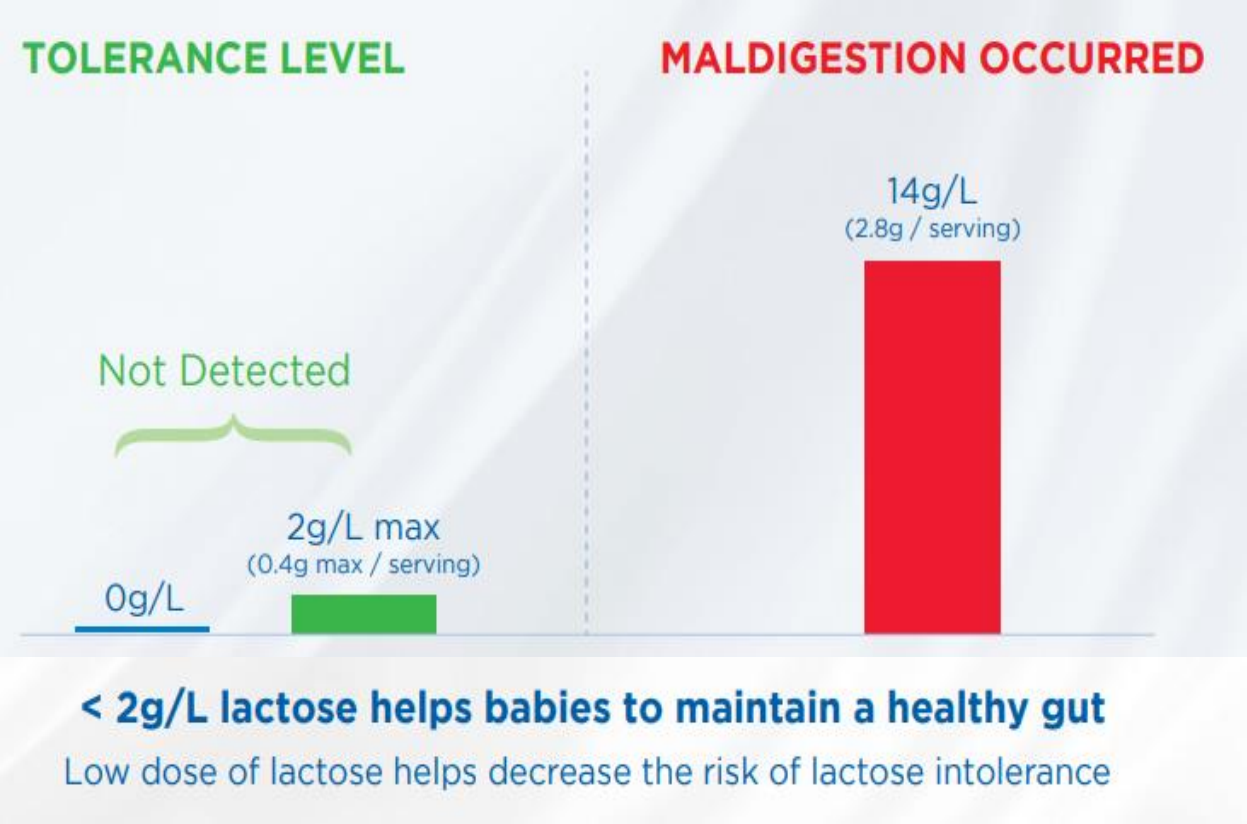
Insufficient Nucleotides

Immune response to nucleotide-supplemented infant formulae: systematic review and meta-analysis

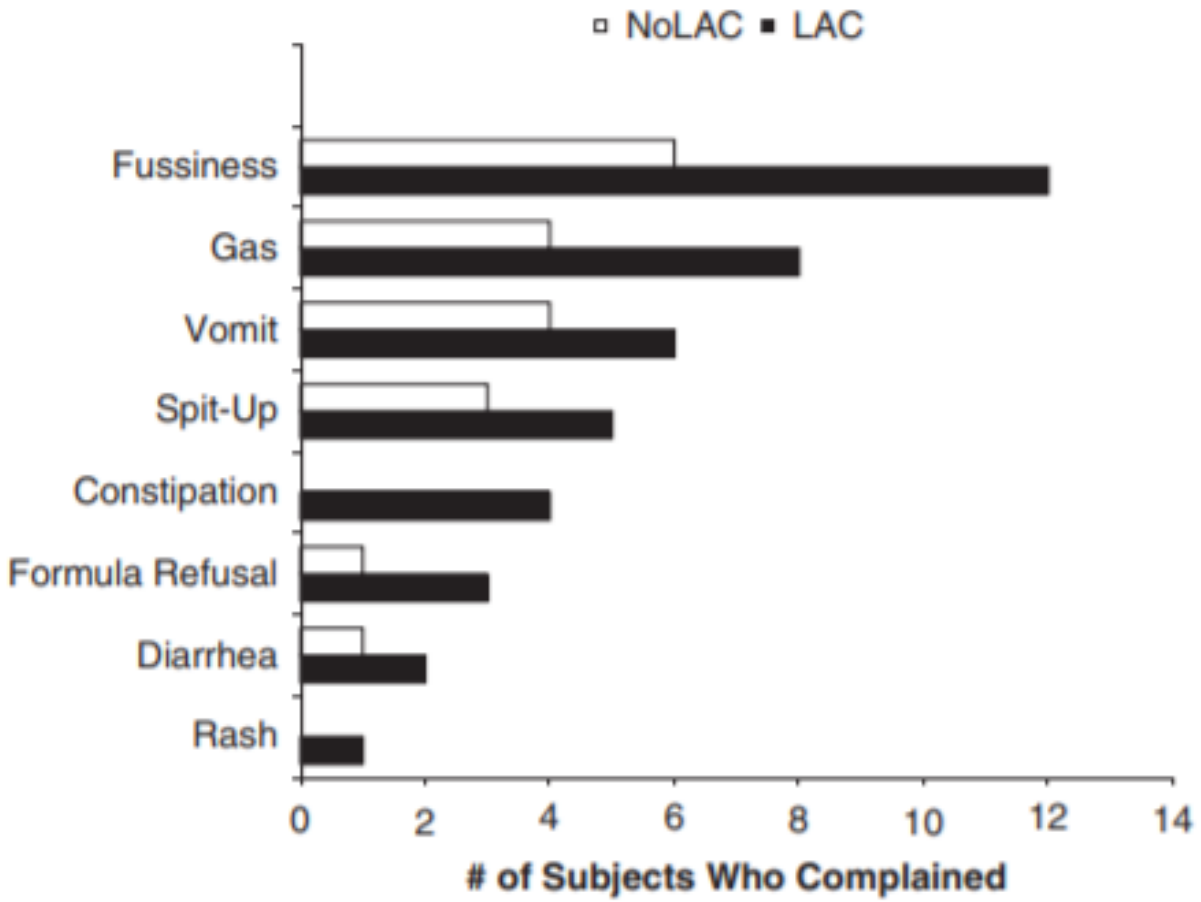
Author	Year	Outcome	Breast Milk group	Nucleotide Fortified group	Control Formula group	*P*
Carver[6]	1991	NK¥ cells (%)	41 ± 4·7	32 ± 3·4	22 ± 2·2	<0·05
		IL-2 ≠ (U/ml)	1·84 ± 0·35	1·52 ± 0·21	0·75 ± 0·21	<0·05
Brunser[7]	1994	Episodes of diarrhoea	**	109	140	<0·05
		Children with first diarrheic episode	**	74	102	<0·05
		Children free of diarrhea (%)	**	45	31	NS
Navarro[9]	1996	IgA (mg/dl) at 20–30 days	**	22 ± 4	10 ± 1	<0·05
		IgA (mg/dl) at three months	**	28 ± 5	20 ± 1	NS
Pickering[12]	1998	Hib-Abs (mg/ml) at 7 months	4·1 ± 1·4	7·2 ± 2·4	4·0 ± 1·5	<0·05
		Diphteria-Abs (mg/ml) at 7 months	1·3 ± 0·3	1·8 ± 0·3	1·4 ± 0·2	<0·05
		Children with diarrhea (%)	13	15	41	<0·05
Ostrom[15]	2002	Hib Abs (mg/ml) at 7 months	3·02 ± 1·8	7·0 ± 3·8	5·6 ± 2·0	<0·05
		Children with URI* reported (%)	65	64	66	
Yau[14]	2003	Children with URI* reported (%)	**	22	20	<0·05
		Children without diarrhea at 24m (%)	**	60	50	NS
Schaler[19]	2004	Oral Polio Virus VN1 Abs at 7 months	886 ± 269	834 ± 343	643 ± 249	<0·05
		Hib Abs (mg/ml) at 7 months	1·87 ± 0·6	1·89 ± 0·51	1·62 ± 0·58	NS
Buck[20]	2004	R0 + T-helper cells at 7 months of age (%)	4·7 ± 1·2	4·8 ± 0·5	4·4 ± 0·7	NS
Hawkes[21]	2005	Diphteria Abs (mg/ml)	**	0·36 ± 0·08	0·27 ± 0·13	<0·05

British Journal of Nutrition (2007), 98, Suppl. 1, S64–S67

Low Lactose formula on intolerance symptoms



Occurrence of formula intolerance symptoms/complaints



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