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Food Allergy: Prevention and Treatment

Cow's Milk Allergy

Module 4.2

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Disclosure

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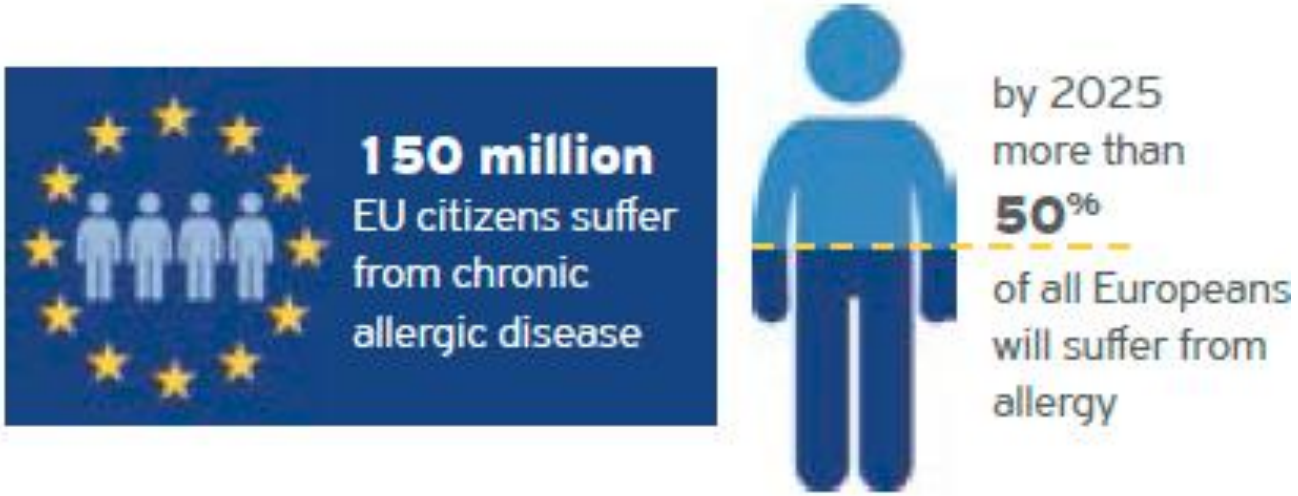
- GlaxoSmithKline
- Takeda
- Hal Allergy
- ALK-Abello
- Yakult
- Teva
- Allergy Therapeutics
- Fagron
- Thermo Fisher Scientific

Allergy Worldwide
a public concern of growing proportions

Allergy Epidemiology



European Academy of Allergy and Clinical Immunology (EAACI) Advocacy manifesto 2016
http://www.eaaci.org/outreach/public-declarations.html

Allergy Epidemiology

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100 million allergic rhinitis
70 million asthma
17 million food allergy (3 million children)

EAACI Advocacy manifesto 2016
http://www.eaaci.org/outreach/public-declarations.html

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In Europe, 1 out of every 20 children has one or more food allergies

Nwaru et al.Allergy. 2014 Aug; 69(8):992-1007

Worldwide rise in food allergy

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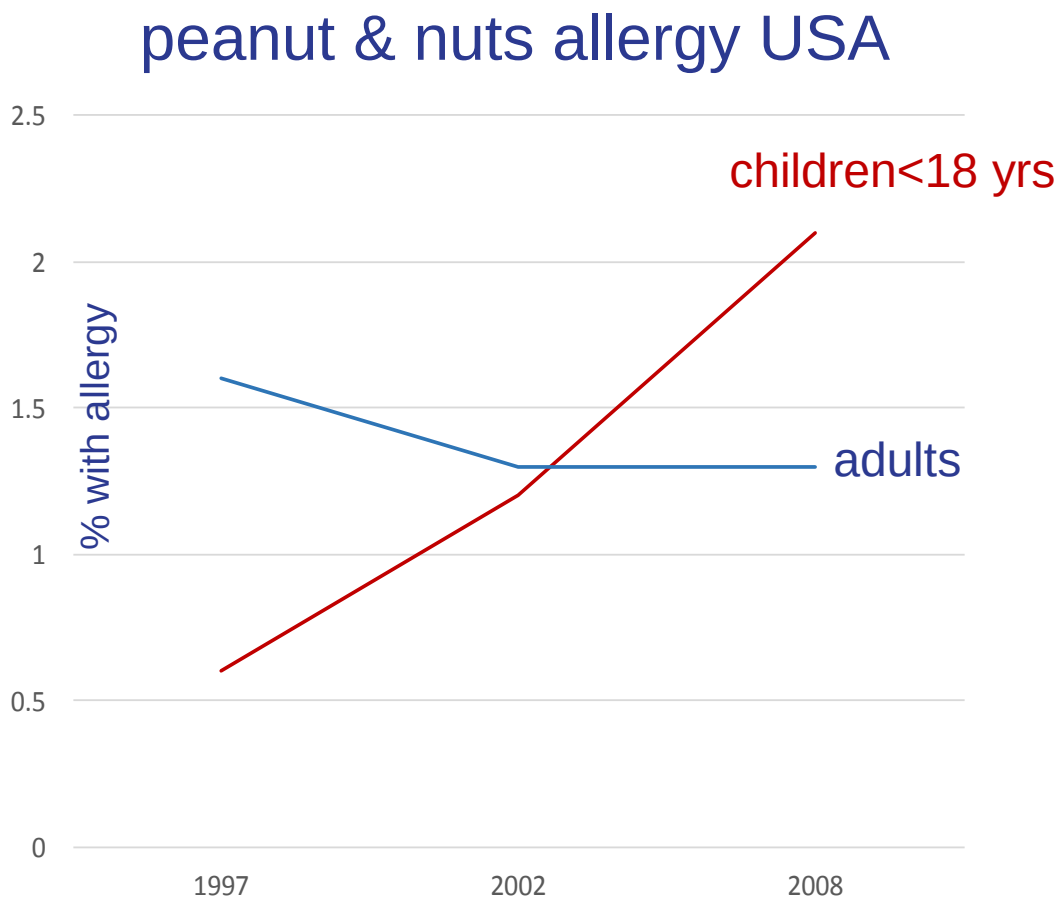
Since ’90’s, 4 fold increase in FA in children

“prevention” FA by delayed introdcution



Sicherer et al, J Allergy Clin Immunol (2010); 125 (6): 1322-1326.

Factors associated with rise in food allergy

	exposition
	late introduction/avoiding of high allergenic foods
	industrial manufacturing of food
	change in eating habits
	skin barrier function
	increase eczema
	dysfunction by increased hygiene
	microbioma
	life style change
	increase caesarean section

EuroPrevall Birth Cohort

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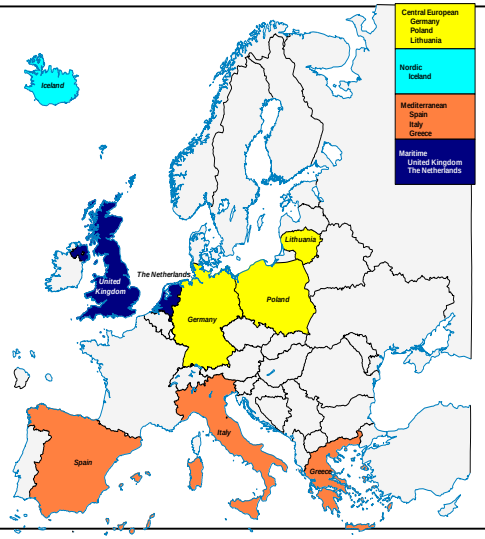
Incidence and immunological mechanisms of Food Allergy Across Europe at 2.5 years

EuroPrevall

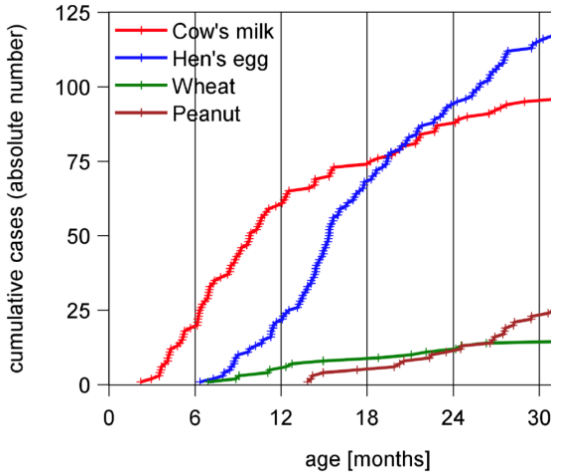
Incidence of FA in Europe



- prospective follow up study
- 13000 infants, case-control

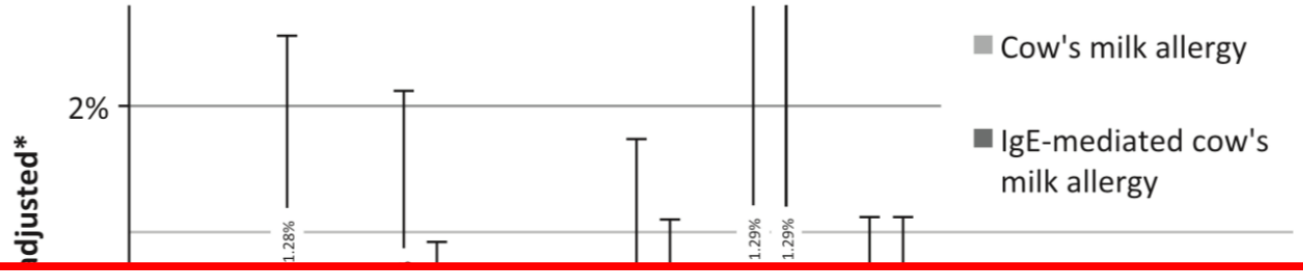
Double blind placebo controlled food challenges

Incidence Food Allergy IgE & non-IgE



Schoemaker et al. Allergy 2015;70:963-72

Cow's milk allergy
EuroPrevall birth cohort



Incidence of challenge-proven CMA 0.54%

National incidences ranging from <0.3% (Lithuania, Germany, Greece) to 1% (NL)

Fenotypes vary across nations

Schoemaker et al. Allergy 2015;70:963-72

Cow's milk allergy
EuroPrevall birth cohort

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Natural history of cow's milk allergy

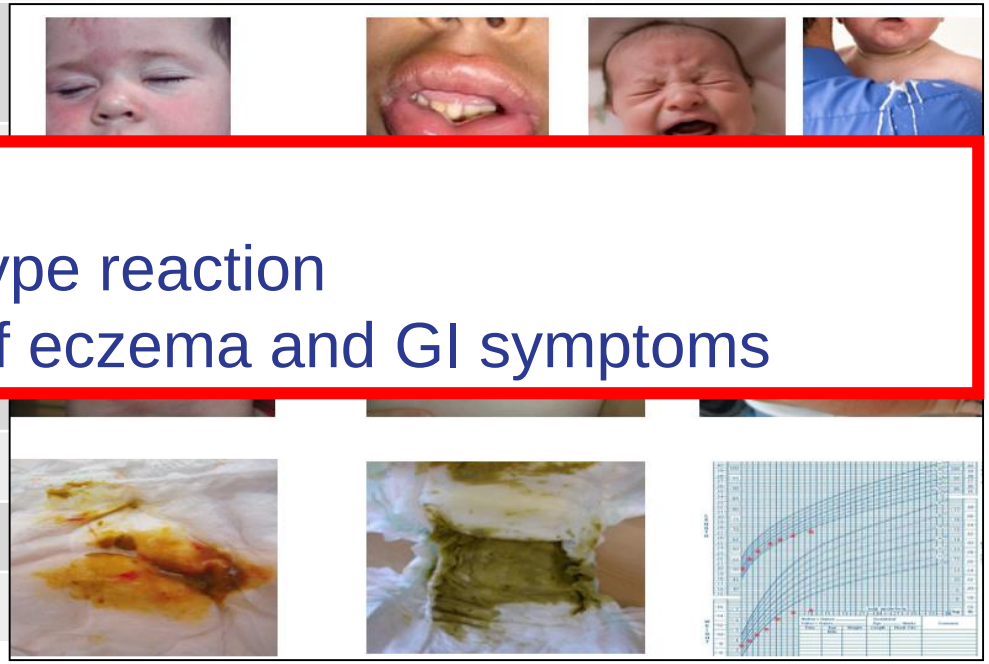
at 12 months, 69% tolerated cow's milk

IgE-mediated CMA – 57%
Non-IgE-mediated CMA – 100%

Schoemaker et al. Allergy 2015;70:963-72

Signs and symptoms of food allergy

Digestive (50-60%)	Skin (5-60%)	Respiratory (20-30%)	General
Dysphagia	Urticaria*	Rhinorrhea	Anaphylaxis*
Regurgitation	Atopic eczema	Wheezing*	
Irritability	Angioedema		
Vomiting*			
Feeding refus			
Poor weight g			
Diarrhea			
Constipation			
Hematochezia			
IDA			



Presentation
- immediate type reaction
- worsening of eczema and GI symptoms

*** Most often seen immediately after exposure and IgE-mediated**

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The prevalence and natural course of food protein–induced enterocolitis syndrome to cow's milk: A large-scale, prospective population-based study

Yitzhak Katz, MD,[a,b] Michael R. Goldberg, MD, PhD,[a] Nelly Rajuan, MSc,[b] Adi Cohen, MD,[a] and Moshe Leshno, MD, PhD[c] *Zerifin and Tel Aviv, Israel*

FPIES

The prevalence (0,34%) of FPIES is significant, and its clinical presentation is distinct from that of IgE-CMA.

Most patients with FPIES recover, although a proportion might convert to IgE-CMA.

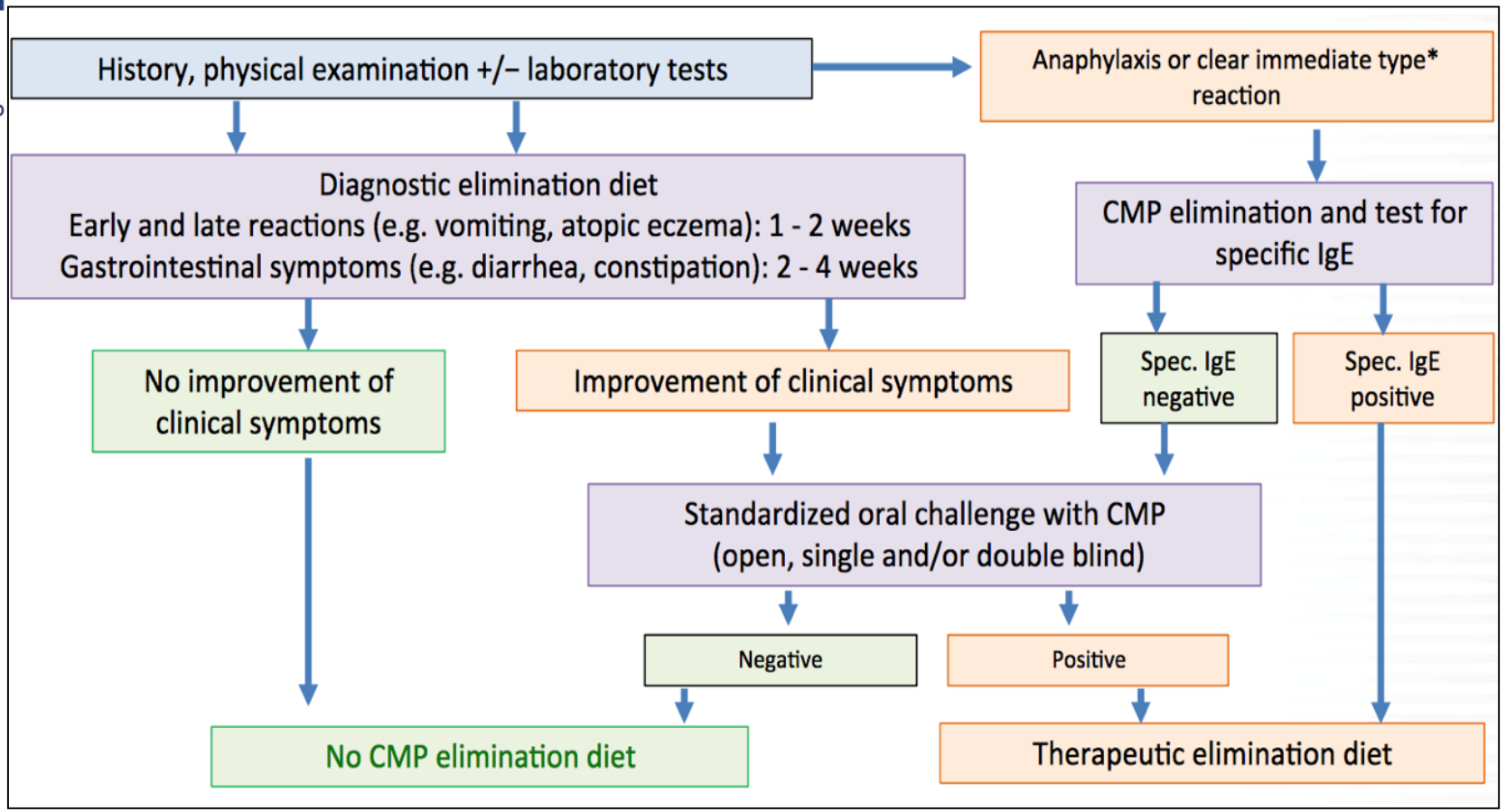
Diagnosis

comparison of approaches proposed by various organizations

	WAO 2010	ESPGHAN 2012	BSACI 2014
History	+	+	+
Physical exam	+	+	+
Oral food challenge	+	+	+
Specific IgE	+	+	sIgE ≥0.35 kU/L to support a clinical dx
Skin prick test	+	+	Wheal ≥5(≥2) mm - predictive
Total IgE	NA	No benefit over specific IgE	NA
Atopy patch test	NA	No	NA
Intradermal tests	NA	No	NA
Specific IgG/IgG subclasses	NA	No	No

NA – not addressed

Diagnosis of CMA ESPGHAN 2012



Koletzko et al. ESPGHAN GI Committee Practical Guidelines. JPGN 2012;55:221-9.

Management

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

2014

POSITION PAPER

EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy

A. Muraro[1,*], T. Werfel[2,*], K. Hoffmann-Sommergruber[3,*], G. Roberts[4,5,6], K. Beyer[7], C. Bindslev-Jensen[8], V. Cardona[9], A. Dubois[10], G. duToit[11,12], P. Eigenmann[13], M. Fernandez Rivas[14], S. Halken[15], L. Hickstein[16], A. Høst[14], E. Knol[17], G. Lack[11,12], M. J. Marchisotto[17], B. Niggemann[7], B. I. Nwaru[18], N. G. Papadopoulos[19,20], L. K. Poulsen[21], A. F. Santos[11,22,23], I. Skypala[24], A. Schoepfer[25], R. Van Ree[26], C. Venter[4], M. Worm[7], B. Vlieg–Boerstra[27], S. Panesar[28], D. de Silva[29], K. Soares-Weiser[30], A. Sheikh[28,31], B. K. Ballmer-Weber[32], C. Nilsson[33], N. W. de Jong[34], & C. A. Akdis[35,36] on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group

	Level of evidence	Grades of recommendation	
(B1) Elimination diet			
A sufficient elimination diet should be based on a formal allergy diagnosis identifying the food allergen(s) responsible of the patient's symptoms/reactions. The indications should be re-evaluated at appropriate intervals	IV	D	(51, 52, 54)
Appropriate dietary avoidance is the key treatment in the management of food allergy	IV	D	Expert opinion
Patients with food allergy who are on long-term elimination diets should have access to appropriate dietetic counseling, ideally by a dietitian with competencies in food allergy, and regular monitoring of growth (in children)	IV	D	Expert opinion
Extensively hydrolyzed cow's milk formulas with documented hypoallergenicity can be recommended as first choice for the treatment of cow's milk allergy, especially in infants and young children. Amino acid formulas can also be recommended especially for the subgroup of patients with more severe symptoms	I	A	(55, 57, 59, 84)
Soy formulas should not be recommended before 6 months of age and at any age in the presence of gastrointestinal symptoms. From 6 to 12 months, it can be considered on a case-by-case basis	I	B	(5)
Currently, probiotic supplements cannot be recommended for the management of food allergy	I	D	(5, 69)

CMA – reference guide to the recommendations

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	1st	2nd

Two main goals:

1.Preventing allergic reactions through allergen avoidance
2.Ensuring optimal nutrition and body growth on the restricted diet.

Berni Canani et al. JPGN 2016

CMP-induced gastroenteritis/proctocolitis	eHF	**AAF**

Not recommended for the management of CMA

- Partially hydrolyzed formula
- Soy formula during the first 6 mo of life, and not at any age in the presence of GI symptoms
- Milk of other mammalian species
  - sheep, buffalo, horse, goat
- Unmodified soy or rice milk
- 'Milk beverages'
  - Based on almond, coconut, hazelnut, oat, potato, rice, soya

Duration of milk exclusion diet

- Re-assessment every 6-12 mo from 12 mo of age
- To assess the possibility of reintroduction of cow's milk protein

Management

- Elimination diet is the current treatment.
- Patients should receive appropriate medication for treatment of accidental reactions.
- Education of allergen avoidance and emergency treatment.
- Re-evaluation at appropriate intervals to determine tolerance development.

Current status
Immunotherapy in food allergy

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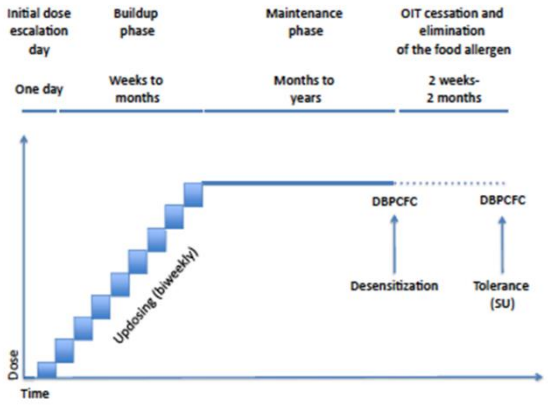
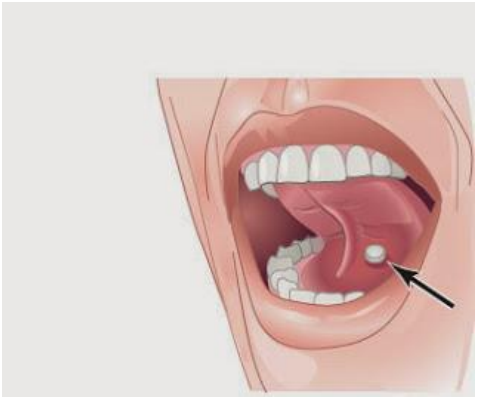
oral

OIT



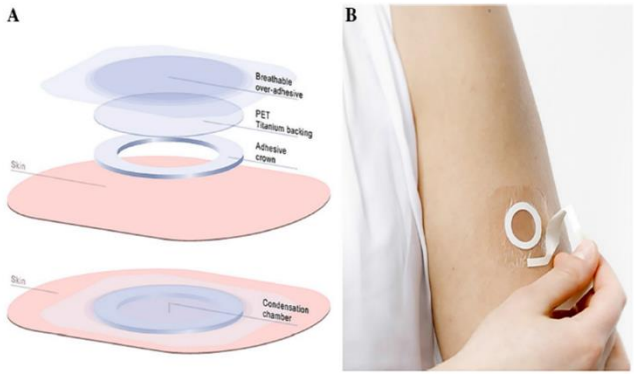
sublingual

SLIT



epicutane

EPIT



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POSITION PAPER

WILEY Allergy

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EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy

Recommendations on efficacy of OIT in children with persistent CMA

Recommendations[a]	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
OIT is recommended as a treatment option to increase threshold of reaction while on treatment in children with persistent cow's milk allergy, from around 4-5 years of age.	I	A	Strong recommendation based on convincing evidence from SR and meta-analysis[18] including RCTs at low[7,9] or unclear risk of bias [44]	Risk of adverse reactions needs to be considered. Age recommendation is based on expert opinion	Nurmatov et al[18]; Longo et al[7]; Pajno et al[9]; Skripak et al[44]
A recommendation cannot currently be made for OIT as a treatment option in children with persistent cow's milk allergy with the goal of post-discontinuation effectiveness	I	B	Weak as only one small RCT at high risk of bias[40]	Further studies needed	Staden et al[40]

[a]OIT for food allergy should only be undertaken in highly specialized clinical centers with expertise and facilities to safely deliver this therapy.

Pajno et al. Allergy 2017

Clinical Commentary Review

JACI 2017

There are no currently FDA/EMA approved therapies for FA

AR101 peanut PALISADE STUDY(Aimmune) and Viaskin Peanut REALISE STUDY (DBV Technologies) are Phase 3 clinical, both have:

FDA Breaktrough Therapy Designation Status

Christopher P. Parrish[1] · Daniel Har[1] · J. Andrew Bird[1]

Published online: 22 February 2018

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Immunotherapy
Oral tolerance induction

- **Problems/limitations**
  - Long-term tolerance?
  - Risk of adverse effects

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Take home messages so far

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- **Food allergy**
  - a global health issue with increasing prevalence (but differences between countries exist)
- **Diagnosis**
  - history, diagnostic elimination diets followed by oral challenge test, SPT, specific IgE
- **Treatment**
  - strict avoidance of the offending allergen
- **Oral immunotherapy**
  - not yet recommended for routine practice

Prevention

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Early nutritional strategies for preventing allergic disease

- Exclusive breastfeeding
- Use of dietary products with reduced allergenicity
- Early *vs.* delayed introduction of complementary foods
- Probiotics, prebiotics

Breastfeeding & Allergy
What is the evidence?

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- No association
- A reduced risk
- An increased risk

The issue remains controversial 10

What to advice?

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Exclusive breastfeeding is recommended for all infants for the first 4- 6 months

ESPGHAN Committee on Nutrition. JPGN 2009;49(1):112-125.
AAP. Pediatrics 2012;129;e827
EAACI Food allergy and Anaphylaxis guidelines. Primary prevention of food allergy. Allergy 2014; 69: 590-601

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Use of dietary products with reduced allergenicity

Published meta-analyses

	Cochrane review 2006	Szajewska CMRO 2010	Alexander JPGN 2010	Boyle BMJ 2016
Search date	2006	2010	2010	2016
Studies	RCT only	RCT only	RCT & CT	RCT/CT
	All HF	Only pHF-W	Only pHF-W	All HF
Main conclusions	HF compared to a CMF reduces infant and childhood allergy and infant cow's milk allergy	pHF-W compared to CMF was effective in allergy prevention in children at high risk for allergy at most time points.	PHF-W instead of CMF reduces the risk of AD in infants, particularly in infants with a family history of allergy	No consistent evidence to support the use of hydrolyzed formula for the prevention of allergy

RCT, randomized controlled trial; CT, controlled trial; HF, hydrolyzed formula; pHF(W), partially hydrolyzed formula (whey)

Hydrolyzed formulas Recommendations

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Organisation	Risk	Recommendation (if not breast-fed)
ASCIA 2016	No consistent convincing evidence to support a protective role for partially hydrolyzed formulas	
EAACI 2014	At-risk	Hydrolyzed formula
CSACI 2013	At-risk	Hydrolyzed formula
AAAAI 2013	At-risk	Hydrolyzed formula
US NIAID 2010	At-risk	Hydrolyzed formula

EAACI = European Academy of Allergy and Clinical Immunology
CSACI = Canadian Society of Allergy and Clinical Immunoloogy
AAAAI = American Academy of Allergy, Asthma & Immunology
NIAID = National Institute of Allergy & Inf Dis
ASCIA, = Australasian Society of Clinical Immunology and allergy

Chan et al. 2013
Boyce et al. JACI 2010;126:S1-S58
Greer FR, et al. *Pediatrics.* 2008;121:183-191.
Høst A, et al. *Pediatr Allergy Immunol*. 2008;19:1-4.
Høst A, et al. *Arch Dis Child.*1999; 81:80-84.

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Early *vs.* delayed introduction of complementary foods & potentially allergenic foods

Timing of introduction of allergenic foods to infants

Recommendations

Ref.	Solid food	Avoidance or delayed introduction of potentially allergenic foods	
		No risk of allergy	Infants at risk
EAACI 2014	4 to 6 mo	No	No
CSACI 2013	4 to 6 mo	No	No
AAAAI 2013	4 to 6 mo	No	No
US NIAID 2010	4 to 6 mo	No	No
AAP 2008	4 to 6 mo	No	No
ESPGHAN 2008	After 17 wk, but not later than 26 wk	No	No

agreement:
No convincing scientific evidence
that the avoidance or delayed introduction of potentailly allergenic foods beyond 4-6 mo reduces allergies

Randomized controlled trials

	Population	Intervention
EAT UK	General population	Cow's milk, egg, peanuts, fish, sesame, wheat
LEAP UK	High risk	Peanuts
HEAP Germany	General population	Hen's egg
PEAAD Germany	High risk	Peanut
PETIT Japan	High risk	Hen's egg
STAR Australia	High-risk infants	Hen's egg
STEP Australia	Moderate risk	Hen's egg

Grimshaw et al. Arch Dis Child 2016

LEAP study
early introduction of peanut

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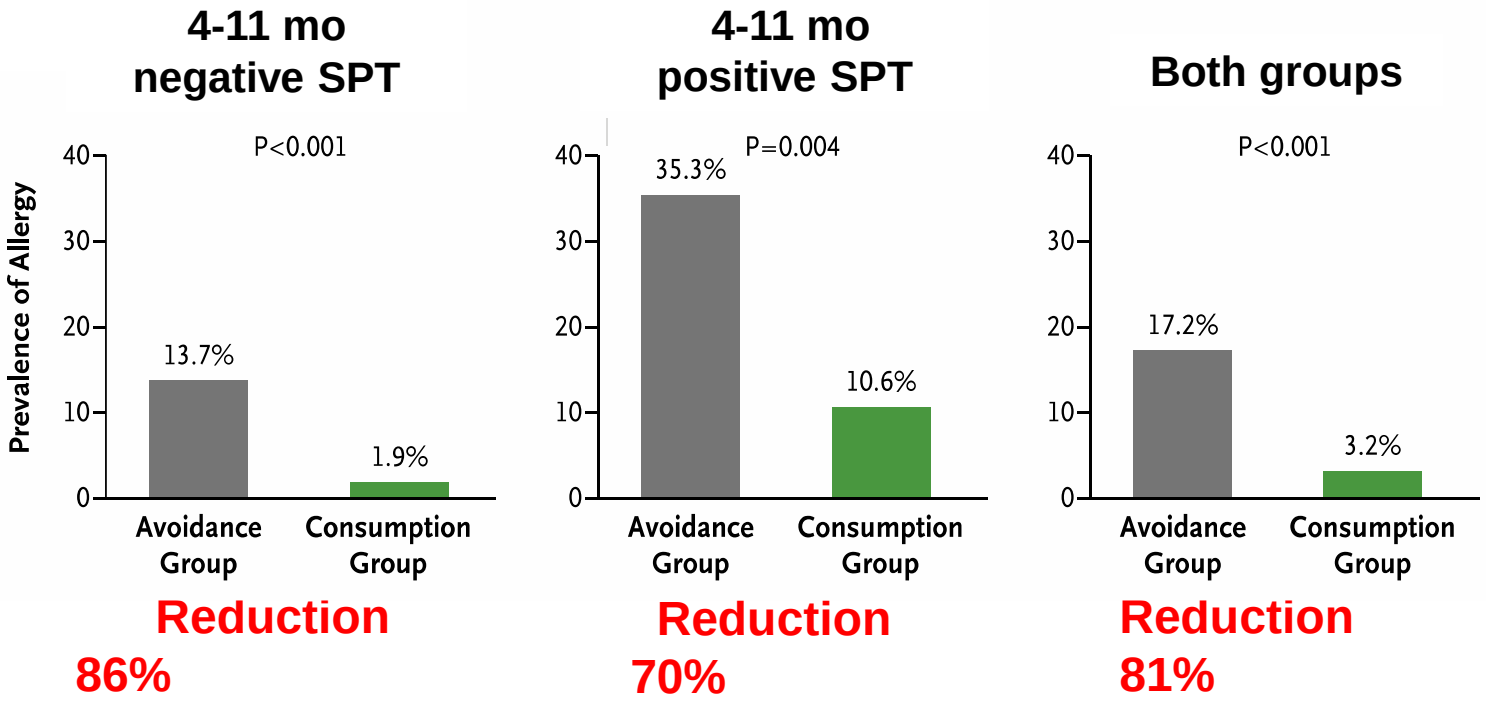
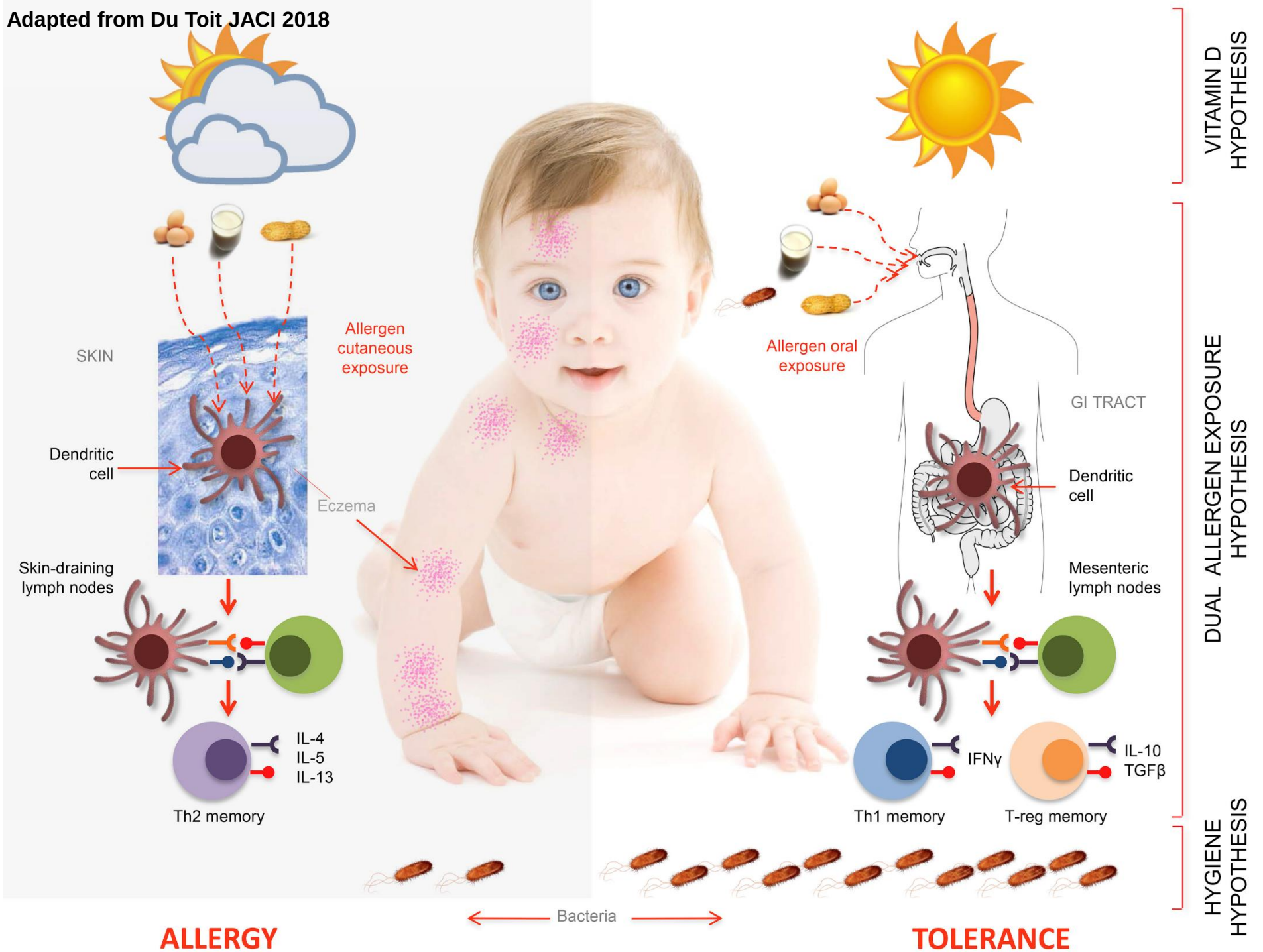
Infants with moderate-severe eczema:
Peanut introduction at 4-11mo or avoidance until 5 yrs



Du Toit et al, NEJM (2015); 372: 803-813


Adapted from Du Toit JACI 2018
VITAMIN D HYPOTHESIS
DUAL ALLERGEN EXPOSURE HYPOTHESIS
HYGIENE HYPOTHESIS
SKIN
Allergen cutaneous exposure
Dendritic cell
Eczema
Skin-draining lymph nodes
IL-4
IL-5
IL-13
Th2 memory
Allergen oral exposure
GI TRACT
Dendritic cell
Mesenteric lymph nodes
IFNγ
IL-10
TGFβ
Th1 memory
T-reg memory
Bacteria
ALLERGY
TOLERANCE

Prevention of peanut allergy – Current recommendations

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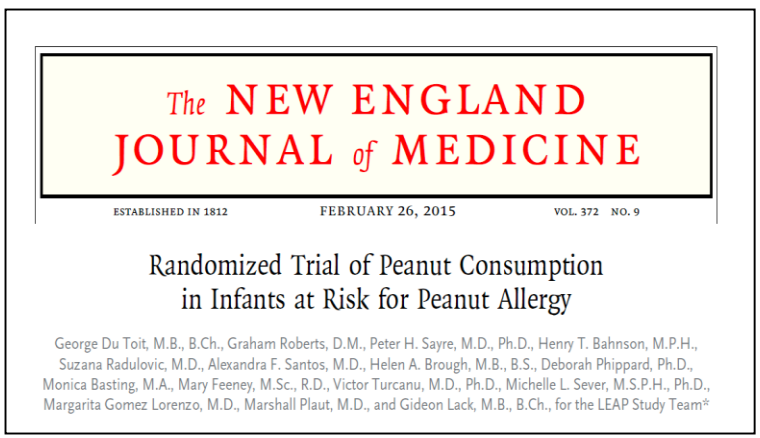
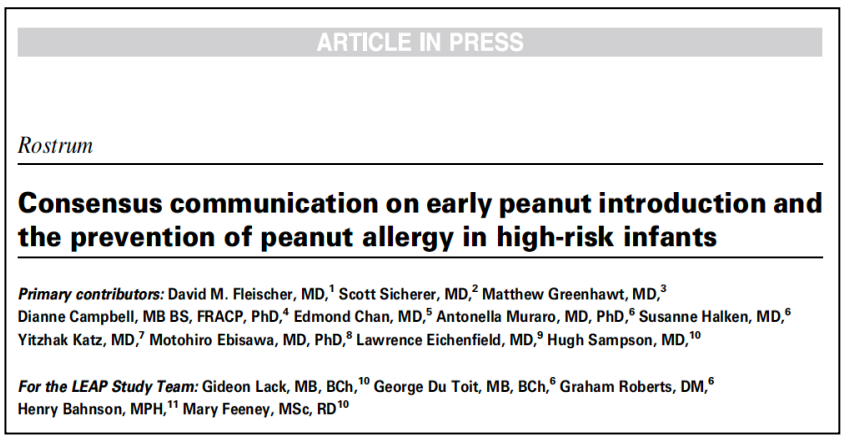


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 26, 2015 VOL. 372 NO. 9

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*



ARTICLE IN PRESS

Rostrum

Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants

Primary contributors: David M. Fleischer, MD,[1] Scott Sicherer, MD,[2] Matthew Greenhawt, MD,[3] Dianne Campbell, MB BS, FRACP, PhD,[4] Edmond Chan, MD,[5] Antonella Muraro, MD, PhD,[6] Susanne Halken, MD,[6] Yitzhak Katz, MD,[7] Motohiro Ebisawa, MD, PhD,[8] Lawrence Eichenfield, MD,[9] Hugh Sampson, MD,[10]

For the LEAP Study Team: Gideon Lack, MB, BCh,[10] George Du Toit, MB, BCh,[6] Graham Roberts, DM,[6] Henry Bahnson, MPH,[11] Mary Feeney, MSc, RD[10]

..health care professionals should recommend introducing peanut-containing products into the diets of "high-risk" infants early on in life (between 4 and 11 mo of age) in countries where peanut allergy is prevalent because delaying the introduction of peanut can be associated with an increased risk of peanut allergy.

Fleischer et al. J Allergy Clin Immunol. 2015

NIAID guideline introduction peanut

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NIH National Institute of Allergy and Infectious Diseases

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group	age	recommendation
severe eczema and/or egg allergy	4-6 mnd	consider sensitization assessment and oral food challenge in specialized center
mild-moderate eczema	6 mnd	introduction peanut
no eczema, no food allergy	6 mnd	introduction peanut

Togias et al, JACI 2017; 139: 29

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An Australian Consensus on Infant Feeding Guidelines to Prevent Food Allergy: Outcomes From the Australian Infant Feeding Summit

- Start weaning 4-6 mo, continue breastfeeding
- Introduce peanut, boiled egg, cow's milk, wheat before 12 mo (without evaluation)
- Hydrolysed formula's not recommended in prevention of allergy

J Allergy Clin Immunol Pract 2017; S2213-2198(17)

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Complementary food including allergenic foods in 2018

- No evidence that the avoidance or delayed introduction of allergenic foods beyond 4-6 mo reduces allergies.

- Infants at high risk of peanut allergy (those with severe eczema, egg allergy or both) should have peanut introduced between 4 and 11 months.

Up-dated guidelines from WAO, EAACI, ESPGHAN & other organisations are pending

The Netherlands, June 2018: Early introduction peanut and egg

Probiotics for allergy prevention

	EAACI 2014	WAO 2015
Allergy	**No**	**No**
Eczema	Not addressed	There is a likely net benefit from using probiotics resulting primarily from prevention of eczema.
		The WAO guideline panel suggests using probiotic in: •**pregnant** women at high risk for having an allergic child •**infants at high risk** of developing allergy

Conditional recommendations. Very low quality evidence.

Muraro et al. Allergy 2014
Fiocchi et al. WAO Journal 2015:8:4

Prebiotics for allergic disease

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POSITION ARTICLE AND GUIDELINES Open Access

World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Prebiotics

Should prebiotics be used in the prevention of allergy in:	Recommendation
Pregnant women	No recommendation
Breast-feeding mothers	No recommendation
Exclusively breastfe	
Non-exclusively b	

Which prebiotic to use?
When to start?
When to stop?

Cuella-Garcia et al. WAO Journal 2016;9:10

Take home messages

- **Prevention**
  - **Exclusive breastfeeding**
    - 6 mo is a desirable goal (at least 4 mo)
  - **Protein hydrolysates**
    - only formulas with **documented effect**
  - **Complementary foods**
    - No evidence that the avoidance or delayed introduction of allergenic foods beyond 4-6 mo reduces allergies.
    - Infants at high risk of peanut allergy (those with severe eczema, egg allergy or both) should have peanut introduced between 4 and 11 months.

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Case scenario

Case scenario
Clinical presentation

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Presenting symptoms of a 6-month-old boy

- Severe vomiting (6-7 episodes) for the past 2 days
- Symptoms developed within 2 hrs of first introduction of complementary food prepared using cow's milk
- Refusal of feeds
- Irritability

Case scenario
Clinical presentation

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History

- Full term infant
- Unremarkable delivery
- Birth weight – 3.5 kg
- Exclusively breastfed for first 6 mo

Family history

- Maternal history of allergic asthma
- Father allergic rhinoconjunctivitis

Case scenario
Clinical presentation

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Physical examination

- No fever
- Body weight – normal of age (50th pc)
- Conscious but lethargic
- Fair hydration, skin turgor normal
- No rash
- No wheezing
- No pale skin, gums or nails
- Remainder of exam is non-contributory

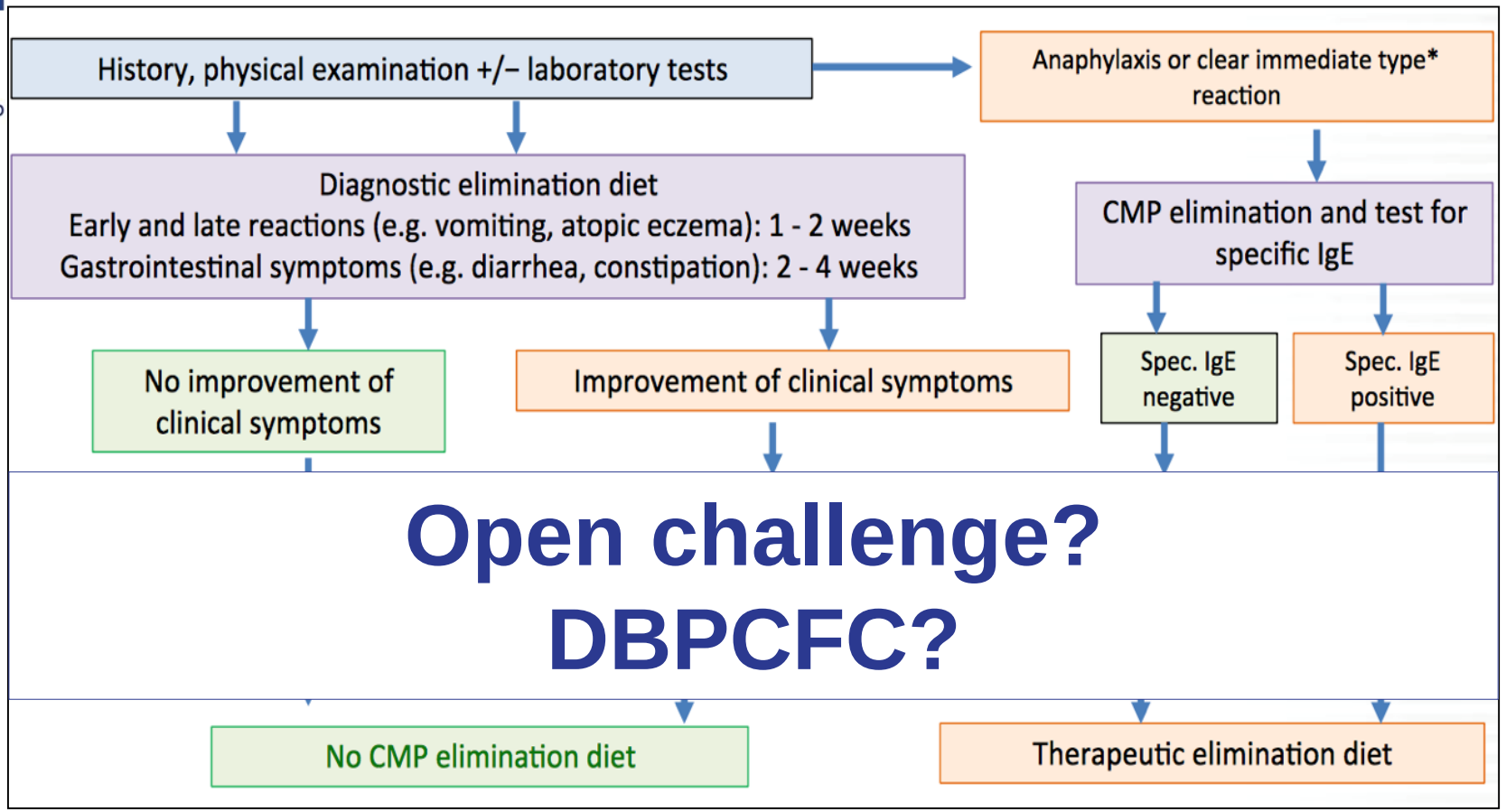
What is your differential diagnosis?

Signs and symptoms of CMA

Digestive (50-60%)	Skin (5-60%)	Respiratory (20-30%)	General
Dysphagia	Urticaria*	Rhinorrhea	Anaphylaxis*
Regurgitation	Atopic eczema	Wheezing*	
Irritability	Angioedema*	Chronic cough	
Vomiting*			
Feeding refusal			
Poor weight gain			
Diarrhea			
Constipation			
Hematochezia			

What should be the diagnostic approach for this infant?

Diagnosis



Koletzko et al. ESPGHAN GI Committee Practical Guidelines. JPGN 2012;55:221-9.

How to proceed in clinical practice

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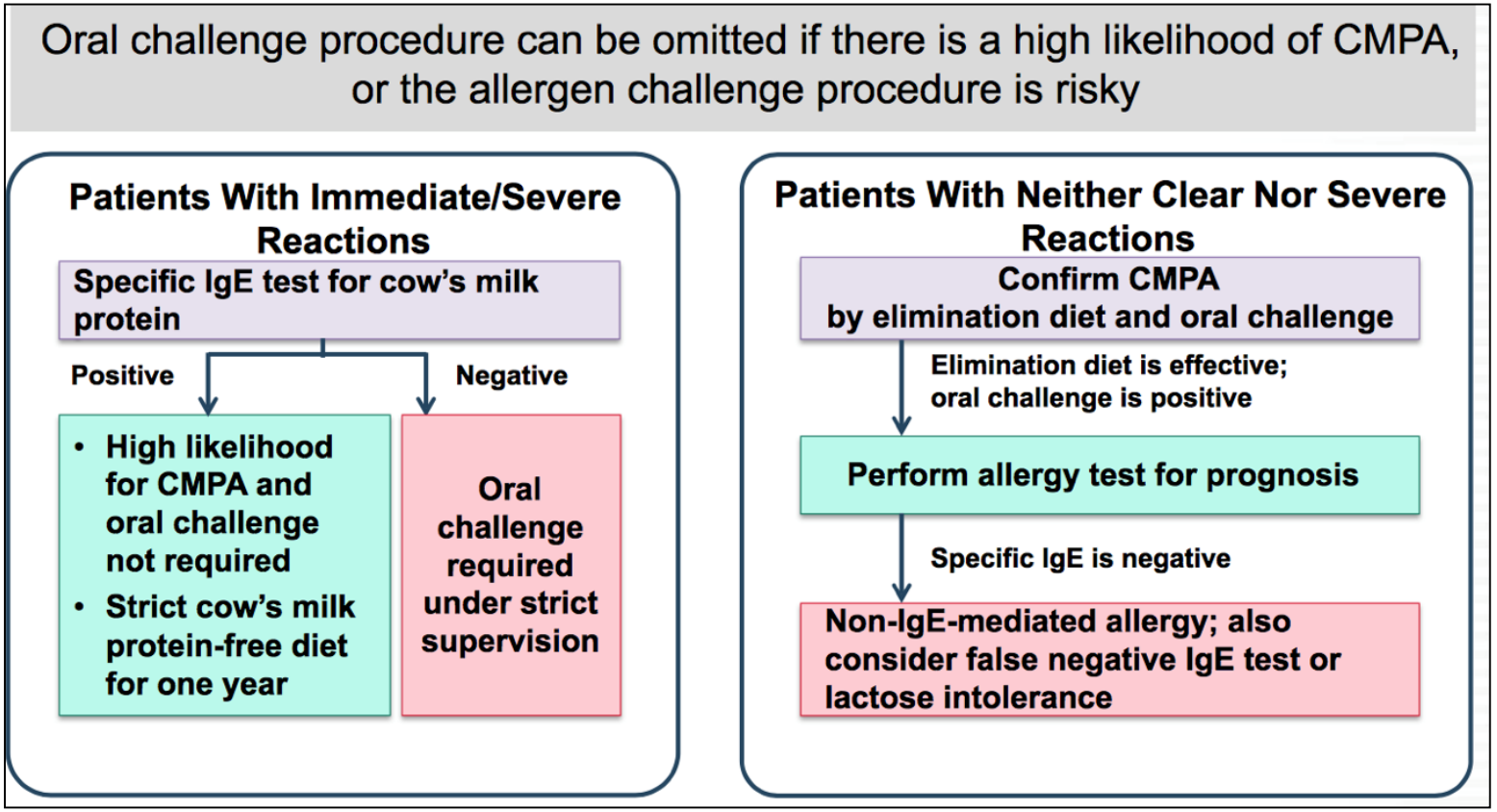

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Case scenario
Discussion about diagnostic approach

Test	Needed?
Skin prick test for cow's milk protein	
Diagnostic elimination of cow's milk	
DBPCFC	
Specific IgE	

Case scenario
Discussion about diagnostic approach

Test	Needed?	Results
Skin prick test for cow's milk protein		Positive
Diagnostic elimination of cow's milk		No refusal of feeds No vomiting
DBPCFC		Positive
Specific IgE		Positive

What are the treatment options in case of confirmed CMA?

Reference guide to the recommendations

Clinical presentation	1st choice	2nd choice
Anaphylaxis	**AAF**	eHF
Acute urticaria or angioedema	eHF	AAF/SF
Severe irritability (colic)	eHF	**AAF**
Constipation	eHF	**AAF**

Two main goals:

1.Preventing allergic reactions through allergen avoidance

2.Ensuring optimal nutrition and body growth on the restricted diet.

Berni Canani et al. JPGN 2016

Growth and nutritional concerns in children with food allergy

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Studies have raised concerns about poor diet and nutritional deficiencies in children following avoidance diets

ARTICLE IN PRESS

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Growth Comparison in Children with and without Food Allergies in 2 Different Demographic Populations

Harshna Mehta, MD, Manish Ramesh, MD, PhD, Elizabeth Feuille, MD, Marion Groetch, MS, RD, and Julie Wang, MD

Monitoring growth and guiding food allergic patients in choosing appropriate alternatives is crucial

Mehta et al. Curr Opin Allergy Clin Immunol 2013
Mehta et al. J Pediatr 2014

Case scenario
Management and follow-up

- Cow's milk protein free diet for 1 y
- eHF (as BF was not possible)

Case scenario
Management and follow-up

- Cow's milk protein free diet for 1 y
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- GI symptoms re-appeared

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Management and follow-up

- Cow's milk protein free diet for 1 y
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- Soy protein-based formula was given [Do you agree?]

Case scenario
Management and follow-up

- Cow's milk protein free diet for 1 y
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- Soy protein-based formula was given [Do you agree?]
- Plan was to continue elimination diet for 1 y [Do you agree?]

Case scenario
Management and follow-up

- Cow's milk protein free diet for 1 y
- eHF (as BF was not possible)
- GI symptoms re-appeared
- Soy protein-based formula was given [Do you agree?]
- Plan was to continue elimination diet for 1 y [Do you agree?]
- Calcium supplements to be considered [Do you agree?]

Case scenario
Management and follow-up

- Cow's milk protein free diet for 1 y
- eHF (as BF was not possible)
- GI symptoms re-appeared
- Soy protein-based formula was given [Do you agree?]
- Plan was to continue elimination diet for 1 y [Do you agree?]
- Follow-up visit scheduled after 1 y to reassess the tolerance. [Do you agree?]

Take home messages

- **Food allergy**
  - a global health issue with increasing prevalence (but differences between countries exist)
- **Diagnosis**
  - history, diagnostic elimination diets followed by oral challenge test, SPT, specific IgE
- **Treatment**
  - strict avoidance of the offending allergen
- **Oral immunotherapy**
  - not yet recommended for routine practice

Take home messages

- **Prevention**
  - **Exclusive breastfeeding**
    - 6 mo is a desirable goal (at least 4 mo)
  - **Protein hydrolysates**
    - only formulas with **documented effect**
  - **Complementary foods**
    - No convincing scientific evidence that the avoidance or delayed introduction of allergenic foods beyond 4-6 mo reduces allergies.
    - Infants at high risk of peanut allergy (those with severe eczema, egg allergy or both) should have peanut introduced between 4 and 11 months.