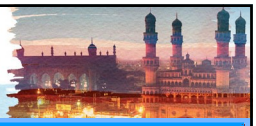
WISC 2012 Hyderabad, India 6-9 December

2012 WAO International Scientific Conference

A World Federation of Allergy Asthma and Clinical Immunology Societies



Recent advances in diagnosis and oral food challenge tests: oral food challenges

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The Bambino Gesù Paediatric Hospital,
Rome, Vatican City State

Hyderabad, December 6th, 2012

Educational objectives

At the end of this lecture, participants will be able to:

Understand the rationale behind the use of different tests for the diagnosis of food allergy

Identify the best way patient by patient

Assess the impact of a correct diagnosis on treatment of food allergy

Conflict of interest

Speakers' Bureau: none

Advisory boards: ALK-Abellò, Chiesi, Stallergènes Italy

Currently sponsored research: MSD, GSK, Pediatrica, Lombardy Regional Government

Not all children reported have food allergy

1:7 self-reported
1:2 SPT+ve

confirmed at DBPCFC

OFC
+ history
+ SPT

.6 %

Courtesy of Gualtiero Leo MD

ce of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. Pediatr Allergy Immunol. 2006;17:356-63

NIH guidelines for the diagnosis and management of food allergy

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

Gu… **oral food chall…** is the "gold stan… challenge may b… nical setting when… ptoms (i.e., nega… e objective sympto… correlate with medica… oratory tests.

http://www.niaid.nih.gov/topics/foodAllergy/clinical/Documents/guidelines.pdf

Oral food challenges

When
Open, single-blind, double-blind?
Preparing the patient
Preparing the food
Choosing the placebo
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Particular situations
Conclusions

Indications for food challenges

1. Identify foods causing acute reactions for initial diagnosis of food allergy and for monitoring resolution of food allergy
2. Determine whether food allergens associated with chronic conditions such as atopic dermatitis or allergic eosinophilic esophagitis will cause immediate reactions
3. Expand the diet in persons with multiple dietary restrictions, usually because of subjective complaints such as headaches or hyperactive behavior
4. Assess the status of tolerance to cross-reactive foods
5. Assess the effect of food processing on food tolerability

(eg, fruits and vegetables that may be tolerated in cooked form in the pollen-food allergy syndrome)

Nowak-Wegrzyn A, Assa'ad AH, Bahna SL. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123(6 Suppl):S365-83

Benefits of food challenges

If positive:

- a conclusive diagnosis of food allergy demonstrating the need for continued strict avoidance
- reduction of the risk of inadvertent exposures
- reduction of anxiety about the unknown
- validation of the patients and families efforts to avoid a food.

If negative:

- expansion of the diet
- improvement of the patient's nutrition and quality of life.

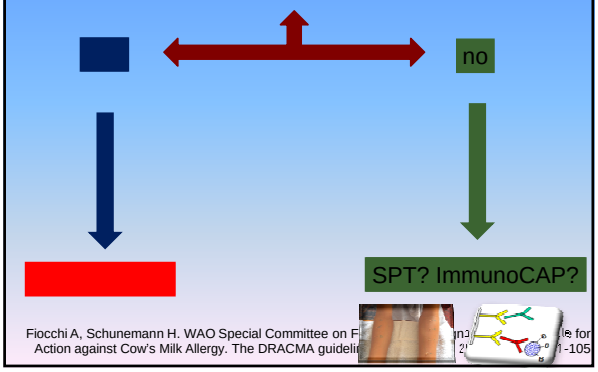
Nowak-Wegrzyn A, Assa'ad AH, Bahna SL. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123(6 Suppl):S365-83

Risks of food challenges

Challenges are time consuming, expensive and may cause severe clinical reactions including life-threatening anaphylactic reactions. It would be desirable to have a simple diagnostic test that could render resource-consuming oral food challenges unnecessary.

Verstege A. The predictive value of the skin prick test weal size for the outcome of oral food challenges. Clin Exp Allergy 2005; 35:1220-6

Can we perform OFC ?



Fiocchi A, Schunemann H. WAO Special Committee on F… Action against Cow's Milk Allergy. The DRACMA guideli… 2… …1-105

Risk assessment

High Medium Low

- How many organs does the reaction involve?
- How immediate is the reaction?
- How severe are symptoms?

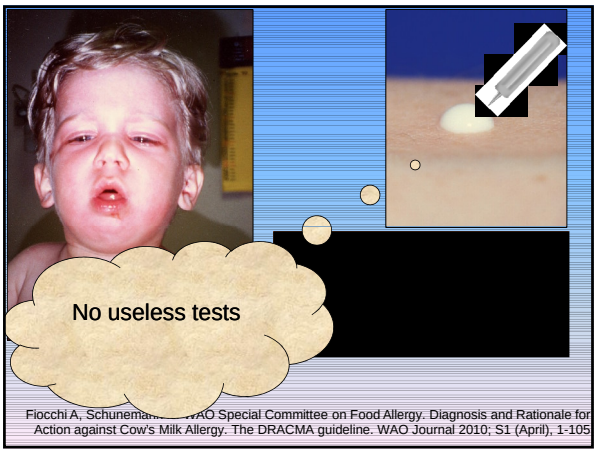
Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow's Milk Allergy. The WAO DRACMA guideline. WAO Journal & Pediatr Allergy Immunol 2010; *S1 (April), 1-105.*

Question 1

Should *skin prick tests be used for the diagnosis of* IgE-mediated cow's milk allergy (CMA) in patients suspected of CMA?

- R: If oral food challenge required for IgE mediated allergy – do only food challenge and no other tests
- S: **High pretest probability: No food challenge – use SPT with ≥ 3 mm cut-off to diagnose FA**
- S: Average pretest probability - do only food challenge and no other tests to diagnose or rule out FA
- S: Low pretest probability: No food challenges – use SPT < 3 mm to rule out FA

Strong/Conditional Recommendation/Very low/Low quality evidence



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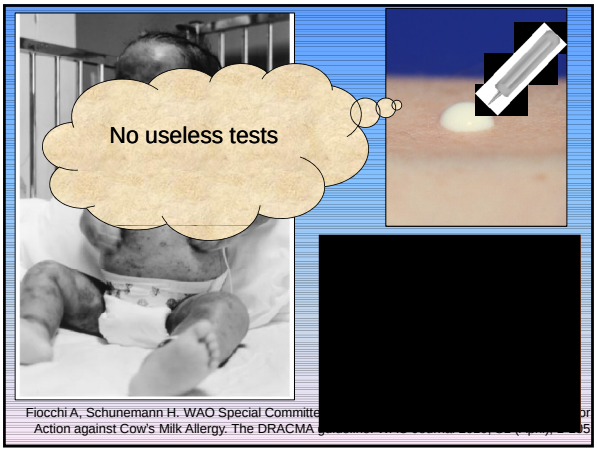

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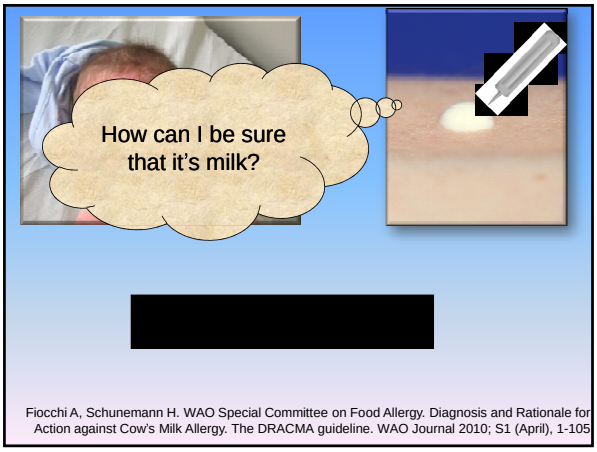

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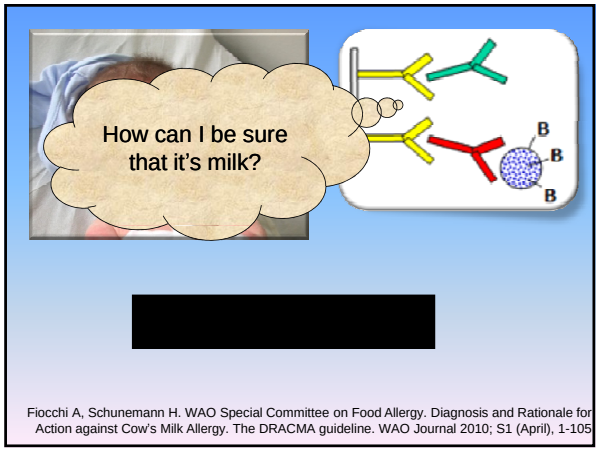

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Oral food challenges

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Which kind of challenge should I administer? Open, single-blind, double-blind?

Courtesy of Sami Bahna

Open or blinded? - I

Clinical situation	*Indication*	*Challenge*	*Setting*
CMA anaphylaxis: not indicated at diagnosis.	Verify every 12 months for assessment of tolerance onset	Open	Hospital
Generalized, important allergic reaction in a single organ (such as urticaria, angioedema, or vomiting, or respiratory symptoms) occurred immediately (within 2 hours after ingestion) with positive CM IgE tests.	Not indicated at diagnosis. Verify every 9-12 months, depending on age, for assessment of tolerance onset	Open	Hospital
Clinical history of Food Protein Enterocolitis from cow's milk with at least one previous episode, both in presence and absence of CMA-specific IgE[6]	Not indicated at diagnosis. Verify every after 18-24 months, for assessment of tolerance onset	Open	Hospital
Moderate to severe atopic dermatitis (AD) resistant to properly done topical therapy for a reasonable period in presence of IgE antibodies to CM.	Indicated	DBPCFC	Hospital

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow's Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105

Open or blinded? - II

Clinical situation	*Indication*	*Challenge*	*Setting*
Clinical situation not suggestive and/or clinical response not immediate (eg. EoE) when patient or her family are convinced of the existence of CMA and thus inclined to interpret any clinical signs as related to cow's milk ingestion .	Indicated	Single-blind (placebo first) or DBPCFC	Hospital
First introduction of cow's milk in CM-sensitised children.	Indicated	Open	Hospital
Reintroduction of cow's milk excluded from the diet for several months on a mere detection of specific IgE in the absence of a suggestive clinical history	Indicated	Open	Hospital
Clinical subjective symptoms (nausea, abdominal pain, itching, oral etc.) after CM ingestion	Indicated	DBPCFC	Hospital
Delayed allergic reaction (eczema, chronic diarrhea, colitis, allergic proctocolitis, gastroesophageal reflux) without CM-specific IgE	Indicated	Open	Hospital or home
In the context of clinical studies	Indicated	DBPCFC	Hospital

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Preparation: stopping treatments before the procedure

Medication	Last dose before OFC
Oral antihistamines	3-10 d
Cetirizine	5-7 d
Diphenhydramine	3 d
Fexofenadine	3 d
Hydroxyzine	7-10 d
Loratadine	7 d
Antihistamine nose spray	12 h
Oral H2 receptor antagonist	12 h
Antidepressants	3 d – 3 wk, drug-dependent
Oral/im/iv steroids	3 d – 2 wk
Leukotriene antagonist	24 h

Nowak-Wegrzyn A, Assa'ad AH, Bahna SL. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123(6 Suppl):S365-83

Preparation: stopping treatments before the procedure

May be continued:

Antihistamine eye drops
Inhaled/intranasal corticosteroids
Topical steroids
Topical pimecrolimus & tacrolimus

Nowak-Wegrzyn A, Assa'ad AH, Bahna SL. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123(6 Suppl):S365-83

Preparation: exclusion diet before challenge

- Avoid all suspected food allergens confirmed at diagnosis
- Lists of acceptable foods and suitable substitutes (for infants)
- Caution with inadvertent ingredients
- Food allergens may come by skin contact
- Food allergens may come as inhalant

Chapman JA. Food allergy: a practice parameter. Annals Allergy Asthma Immunol 2006; 96:S3, 1-68

Tan BM, Sher MR, Good RA, Bahna SL. Severe food allergies by skin contact. Ann Allergy Asthma Immunol. 2001;86:583-6

Roberts G, Lack G. Relevance of inhalational exposure to food allergens. Curr Opin Allergy Clin Immunol 2003;3:211-5

Nowak-Wegrzyn A, Assa'ad AH, Bahna SL. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123(6 Suppl):S365-83

Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow's Milk Allergy. The WAO DRACMA guideline. WAO Journal 2010; S1 (April), 1-105

Venous access pre-challenge?

Milk, wheat: sIgE > 17.5 kU/l

Egg: sIgE > 3.5 kUI/L

Reibel S et al. What safety measures need to be taken in oral food challenges in children?. Allergy 2000;55:940-4

Oral food challenges

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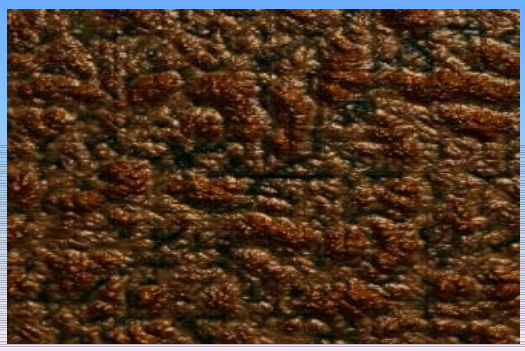
Food preparation: cooking does matter



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The ideal placebo

(1) acceptable taste;
(2) allowance of a challenge dose high enough to elicit allergic reactions in an acceptable volume (most young children are able to consume a maximum challenge dose of about 200 mL of liquid challenge material or 50-100 g of solid food within 15 minutes);
(3) good matching of sensory properties of placebo and active test food recipes
(4) optimal matrix ingredients, including the avoidance of highly allergenic ingredients for possible use in children allergic to multiple foods;
(5) avoidance of the use of frequently suspected foods, such as chocolate;
(6) use of as few ingredients as possible to make recipes acceptable for most patients and to minimize unknown side effects of the ingredients used.

Vlieg-Boerstra BJ. Development and validation of challenge materials for double-blind, placebo controlled food challenges in children. J Allergy Clin Immunol 2004;113:341-6

An ideal placebo

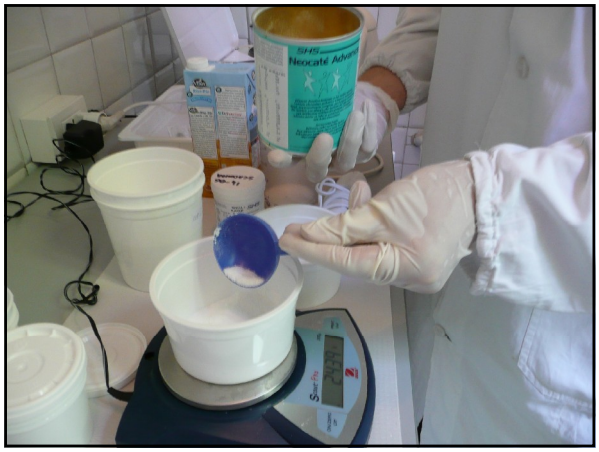
A dessert to blind celeriac and hazelnut

Triangle test

Sufficient blind processing

It can be reproducibly manufactured

Cochrane SA. Development of a standardized low-dose double-blind placebo-controlled challenge vehicle for the EuroPrevall project. Allergy. 2012 ;67:107-13



Which placebo is used in the everyday milk challenge?

Martelli A. Oral food challenges in children in Italy. Allergy 2005; 60:907-11

Oral food challenges

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Food challenges. Initial dose.

Food	Dose
Peanut	0,1 mg
Cow's milk	0,1 mL
Egg	1 mg
Cod	5 mg
Wheat	100 mg
Soy	1 mg
Shrimp	5 mg
Nuts	0,1 mg

Bindslev-Jensen C. Standardization of food challenges in patients with immediate reactions to food – position paper from the European Academy of Allergology and Clinical Immunology. Allergy 2004;59:690-7

Interval between doses

- A time interval of 15–30 minutes is in most cases suitable for IgE-associated reactions unless using capsules
- In published papers, symptoms most often occur 3 to 15 minutes after intake
- Severe reactions always occur immediately
- Patients with suspected late reactions (e.g. exacerbation of AD) continue with intake of normal daily amount the following day settings

Bindslev-Jensen C. Standardization of food challenges in patients with immediate reactions to food – position paper from the European Academy of Allergology and Clinical Immunology. Allergy 2004;59:690-7

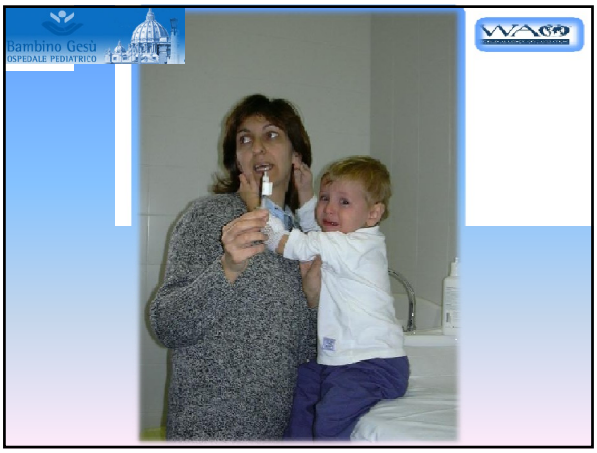
Nowak-Wegrzyn A, Assa'ad AH, Bahna SL. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123(6 Suppl):S365-83

Further doses: three schemes

- Doubling doses until reaction or max dose
- Logarythmic increment: 1, 3, 10, 30, 100 …
- Incremental concentration: 1%, 4%, 10%, 20%, 25%*
- No comparative studies comparing these protocols
- Risk of severe reactions for higher increments
- The top dose should be the normal daily intake in a serving of the food in question, adjusted for the age of the patient.

Bindslev-Jensen C. Standardization of food challenges in patients with immediate reactions to food – position paper from the European Academy of Allergology and Clinical Immunology. Allergy 2004;59:690-7

*AAAAI/ACAAI. Food allergy: a practice parameter. Ann Allergy Asthma Immunol. 2006;96 (3 Suppl 2):S1-68



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Symptoms of food allergy

1014 DBPCFC (in order of rate of occurrence)

- Cutaneous (eczema, urticaria, erythematous rash)
- GI (abdominal pain, vomiting, diarrhea)
- Respiratory (sneeze, rhinorrhea, nasal obstruction, wheezing, cough, ocular sign)
- GI + Cutaneous + Respiratory
- Cutaneous + Respiratory
- GI + Cutaneous
- GI + Respiratory

Bock A. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges.J Pediatr 1990; 117: 561

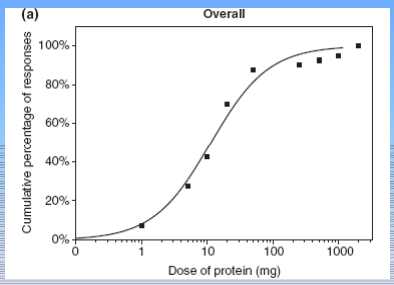
Presentation symptoms vs. reaction at challenge

Table 3. Reaction of Presentation to Reaction of Challenge*

Initial reaction on presentation	Reaction on food challenge				
	Anaphylaxis	Cutaneous	Gastrointestinal	Respiratory	Multiple-organ system
Cutaneous, % (n = 218)	12		8	6	17
Gastrointestinal, % (n = 35)	6	11		3	31
Refusal to eat, % (n = 37)	14	35	14	3	35
Anaphylaxis, % (n = 69)		33	14	6	25
Multiple-organ system, % (n = 40)	12	30	18	5	35
Wheal size, mean ± SEM, mm	10.1 ± 0.59	8.21 ± 0.35	8.67 ± 0.94	7.95 ± 1.5	9.53 ± 0.49
Dose on challenge, mean ± SEM, mL	4.16 ± 1.13†	7.76 ± 1.08	11.2 ± 1.93†	10.8 ± 3.1†	7.82 ± 1.54
Age at challenge, mean ± SEM, y	2.7 ± 0.25	2.8 ± 0.14	3.0 ± 0.25	4.59 ± 0.56‡	1.8 ± 0.20

Spergel J.M. Correlation of initial food reactions to observed reactions on challenges. Ann Allergy Asthma Immunol 2004 ;92 :217-24

Severity of challenge reactions vs severity of reported reactions



Hourihane J. Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? Clin Exp Allergy 2005; 35:1227–33

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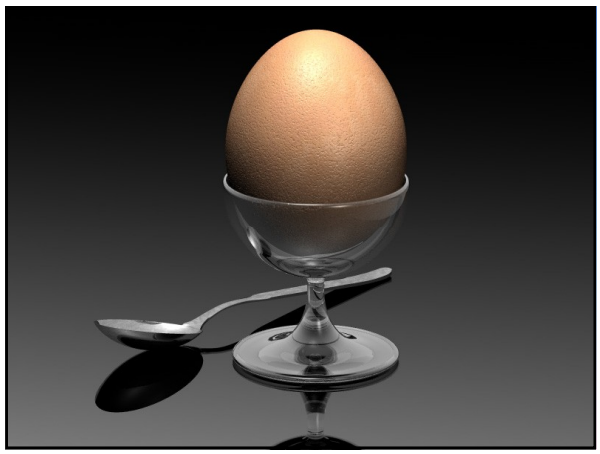
Natural history of nut allergy






It is not possible to establish an half-life for a diagnosis of nut allery. These allergens should be considered as giving indefinitely persistent allergies.

Sicherer SH. Clinical update on peanut allergy. Ann Allergy Asthma Immunol. 2002;88:350-61



Egg allergy –is it forever?

Tolerance reached in:

- 44% of case at 2.5 years
- 31% - 51% at 8 years
- 50% at 35 months
- 66% after 5 years

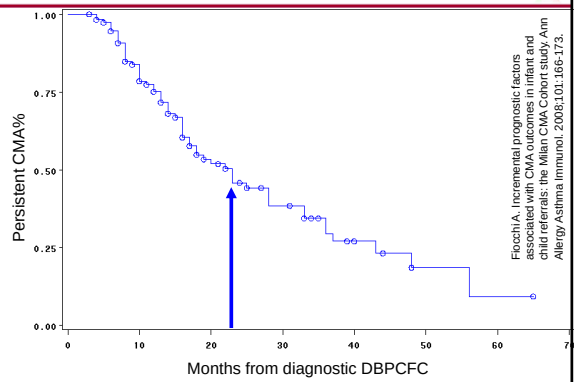
Ford RPK, Taylor B. Natural history of egg hypersensitivity. Arch Dis Child 1982;57:649-52
García Ara MC. Therapeutic aprroach to and prognosis of food allergy. Allergol Immunopathol 1996;24(suppl 1):31-5
Boyano-Martinez T. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. J Allergy Clin Immunol. 2002;110:304-9

Repeating challenges: the MiCMAC flow-chart

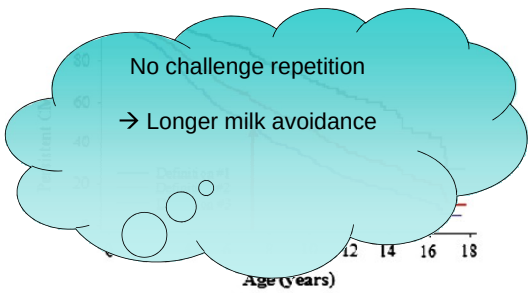
12 months	✓
15 months	
18 months	✓
21 months	
24 months	
27 months	
30 months	✓

Fiocchi A. Incremental prognostic factors associated with cow's milk allergy outcomes in infant referrals: the Milan Cow's Milk Allergy Cohort study. Ann Allergy Asthma Immunol 2008;101:166-73

MiCMAC cohort: survival curve



The Baltimore Cohort – survival curves



Skripak JM. The natural history of IgE-mediated CMA. J Allergy Clin Immunol 2007;120:1172-7

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Challenge through breastmilk

- 17 CMA infants, 10 healthy controls
- All breastfed
- Range 1.8 - 9.4 months
- After strict elimination, high doses of CM to breastfeeding mother
- Verify presence of CMP in breast millk
- 16/17 confirmed with CMA after challenge

Jarvinen KM. Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. J Pediatr 1999;135:506-12.

Jarvinen KM. Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. J Pediatr 1999;135:506-12.

DBPCFEC

A 14-years-old boy
3 episodes of FDEIA following ingestion of meals containing:
a. unpealed sausage;
b. Mascarpone (an italian creamy cheese);
c. artichokes.

All resulted contamined by molds
Penicillium Lanoso-Ceruleum species (PLC) cultured in Agar

Challenges with PLC on separate days

DBPCFC whith PLC food-exercise treadmill ergonometric 120 minutes after a meal containing artichokes, Mascarpone, and sausage

DBPCFEC 120 minutes after four similar meals with the double-blinded addition of doubling doses of PLC solution (0.5, 1, 2, 4 milliliters), or of the excipient as a placebo.

Fiocchi A. Exercise-induced anaphylaxis following food-contaminant ingestion at Double-Blinded, Placebo-Controlled, Food-Exercise Challenge. J Allergy Clin Immunol 1997; 100:424-25

DBPCFEC

DBPCFC with PLC in resting conditions and the food-exercise test after the meal → negative

DBPCFEC was after the meal containing 1 ml of mould solution → positive

Fiocchi A. Exercise-induced anaphylaxis following food-contaminant ingestion at Double-Blinded, Placebo-Controlled, Food-Exercise Challenge. J Allergy Clin Immunol 1997; 100:424-25

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Food Challenge – conclusions

- A sure confirmation of diagnosis
- Threshold
- Variations of sensitization over time
- Exclusion of psychological component (DB)
- Standardisation!
- Experience
- Resources
- Doctor-patient relation

Fiocchi A, Martelli A. The dietary management of food allergy. Pediatr Annals 2006; 14:166-70


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and Clinical Immunology Societies
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