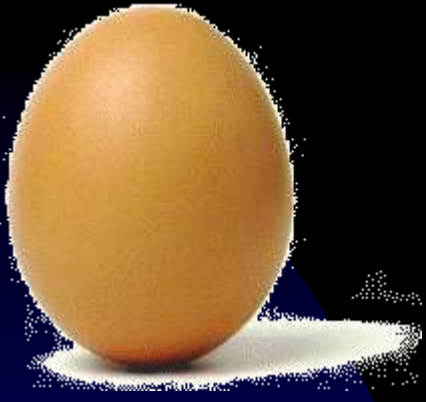


L'Allergia alle proteine dell'uovo, la biologia molecolare e la dieta



- **Calvani Mauro**
- Azienda Ospedaliera S. Camillo-Forlanini
- U.O.C. per il Governo Clinico in Pediatria
 - ed Ematologia Pediatrica
 - Roma



6^o CORSO
NOVITÀ in
ALLERGOLOGIA
ed **IMMUNOLOGIA**
PEDIATRICA

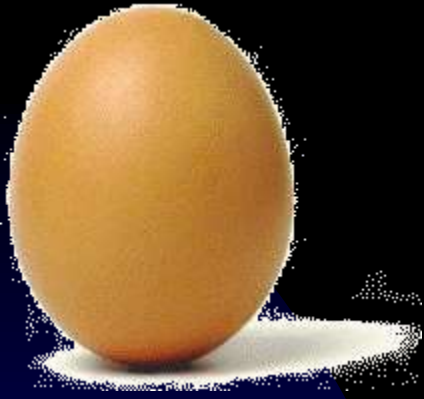
Presidente del Convegno
Francesco Paravati

18 e 19 MAGGIO 2012

Centro Congressi Fra Pietro Maria de Giovanni o.h.
Ospedale Sacro Cuore di Gesù Fatebenefratelli
BENEVENTO

Allattata al seno esclusivamente fino a 5 mesi e mezzo poi svezzamento. Alla introduzione di formaggio plasmon, alla terza somministrazione ha subito manifestato una eruzione cutanea del viso con angioedema dell'occhio, starnuti, rinorrea e difficoltà respiratoria per cui accesso in PS trattata con bentelan e tinset. Sintomi regrediti dopo alcune ore. Dopo 10 giorni la pediatra ha tentato una nuova somministrazione del formaggio mellin con analoga sintomatologia, ma più leggera per rifiuto dal secondo cucchiaino, trattata con bentelan 1 mg. Quindi posta a dieta senza proteine del latte con latte di soia e poichè sospettava allergia ai conservanti del formaggio dopo circa 1 mese ha somministrato del prosciutto cotto con analoga reazione generalizzata alla 3a introduzione, per cui dieta rigorosa senza latte.

A 13 mesi introdotto l'uovo sotto forma di tuorlo cotto, che ha tollerato, ma alla introduzione dell'albume cotto, ha manifestato analoga sintomatologia cutanea e respiratoria, con accesso al PS per cui dieta senza albume ma con tuorlo cotto, senza problemi fino ad ora. Circa 1 mese fa ha introdotto del parmigiano stagionato senza evidenti reazioni, ma nuova reazione generalizzata dopo aver mangiato del formaggio di pecora.



SPT

Lattalbumina = 8 mm

Caseina = 4 mm

Beta lattoglobulina = 6 mm

Albume di uovo = 7 mm

Tuorlo di uovo = 5 mm

Istamina = 6 mm

Controllo = 0 mm

Si consiglia dieta priva di proteine del latte vaccino e latti animali e priva di uovo.

Consentite eventualmente solo le piccole quantità di latte o uovo cotto che fino ad ora ha tollerato

Nel periodo trascorso è stata bene, sempre a dieta senza latte con latte risolac e alcuni biscotti del mulino bianco che contengono tracce di latte e di uovo, senza evidenti reazioni, ha mangiato della cioccolata al latte senza problemi, assume circa $\frac{1}{2}$ del tuorlo dell'uovo cotto, e alcune volte della pasta all'uovo, senza evidenti reazioni

SPT (Novembre 2011)

Lattalbumina = 8 mm
Caseina = 4 mm
Beta lattoglobulina = 6 mm
Albumine di uovo = 7 mm
Tuorlo di uovo = 5 mm
Istamina = 6 mm
Controllo = 0 mm

SPT (Maggio 2012)

Lattalbumina = 4 mm
Caseina = 5 mm
Beta lattoglobulina = 3 mm
Albumine di uovo = 6 mm
Tuorlo di uovo = 4 mm
Ovoalbumina = 6 mm
Ovomucoide = 1 mm
Istamina = 6 mm
Controllo = 0 mm

Si consiglia di continuare la dieta in atto, ovvero con uovo cotto, come fino ad ora consumato, ma senza uovo crudo o in altre forme e dieta senza latte, ma con gli alimenti contenenti tracce

Ulteriore controllo per TPO per il latte



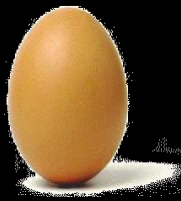
Un uovo di medie dimensioni (60 gr) è costituito da

tuorlo	17 g = 29,8%
albume	22 g = 36,7%
parte non edibile	21 g = 35,5%

Somministrare un tuorlo significa dare circa 1/4 delle proteine che si darebbero somministrando l'albume

% Uovo intero	% Acqua	% Proteine	Kcal
Guscio	8,5-10,5		95
Albume	60-66	10-12	0,5-0,7
Tuorlo	24-30	46	1,1-1,6
Albume + Tuorlo	90-92	74-76	0,3-0,4

UOVO DI GALLINA



Soluzione acquosa di oltre 40 proteine, **almeno 24 frazioni antigeniche diverse**

ALLERGENE	NOME	PREVALENTI NEL
Ovomucoide	Gal d1	albume
Ovoalbumina	Gal d2	albume
Ovotrasferrina	Gal d3	albume
Lisozima	Gal d4	albume
Alfa livetina	Gal d5	albume/carne/epiteli
Vitellogenina	Gal d6	tuorlo
Immunoglobuline	Gal dIgY	albume
Apovitellenina 1	Gal apovitellina I	tuorlo
Apovitellenina VI	Gal d apovitellina VI	tuorlo
Fosvitina	Gal d fosvitina	tuorlo
Ovomucina	Gal d ovomucina	albume
Etc..		



	% albume	Resistenza calore	Resistenza enzimi	Allergene
Ovomucoide (Gal d1)	11	Stabile	Stabile	+++
Ovoalbumina (Gal d2)	54	Instabile	Instabile	++
Ovotrasferrina (Gal d3)	12	Instabile	Instabile	+
Lisozima (Gal d4)	3.4	Instabile	Instabile	++
Alfa-Livetina (Gal d5)	-	-	-	+
Vitellogenina (Gal d6)	-	-	-	+

Da Benhamaou AH, Allergy 2010, modificata

Clinical and immunological study of allergy to hen's egg white VI. Occurrence of protein cross-reacting with allergens in hen's white as studied in egg white from turkey, duck, goose, seagull and in hen egg yolk, and hen and chicken sera and flesh

The occurrence of proteins cross-reacting with allergens in hen's egg white was studied in turkey, duck, goose and seagull egg whites, in hen egg yolk, and in hen and chicken sera and flesh. The study was based upon quantitative immunoelectrophoretic techniques. The different egg whites were all found to contain proteins cross-reacting with most of the allergens in hen's egg white, but the degree of cross-reactivity varied considerably among the various egg whites. All egg whites contained proteins able to bind human IgE-antibody in the sera of patients with allergy to hen's egg white. Several proteins cross-reacting with allergens in hen's egg white were also detected in egg yolk and in hen and chicken sera and flesh. Clinical implications of the results are discussed.

ANAFILASSI DA CONTATTO CUTANEO CON L'UOVO DI QUAGLIA

Caso clinico: Daniele G, bambino di 5 anni, affetto da asma, dermatite atopica e allergico all'uovo (di gallina). Il giorno del compleanno la madre per farlo contento, visto che non può mangiare l'uovo, gli prepara una torta con l'uovo di quaglia, che viene reclamizzato come sicuro per i bambini allergici all'uovo di gallina. Il bambino la aiuta in cucina, e dopo pochi minuti dall'averlo toccato manifesta starnuti, tosse, difficoltà respiratoria, prurito generalizzato e angioedema del viso

	DG	Controlli allergici all'uovo (n 15)	Controlli atopici non allergici all'uovo (n 10)
	Prick by Prick (mm)	Prick by Prick media (mm)	Prick by Prick media (mm)
Bianco Gallina	12	9,2	0
Bianco Quaglia	8	6,9	0
Rosso Gallina	9	5,7	0
Rosso Quaglia	9	5,4	0

La storia “naturale”

The natural history of egg allergy

METHODS

We completed a retrospective chart review of patients with egg allergy. A total of 4958 charts were reviewed, which yielded 881 patients with egg allergy. Patients were included in the chart review if they had a clear clinical history of an IgE-mediated allergic reaction to egg ingestion, or if they had an egg IgE >2 kU/L without known tolerance to egg, typically detected in the evaluation of atopic dermatitis or other food allergies.

TABLE I. Criteria for clinical tolerance

Clinical tolerance definition	Criteria
#1*	Tolerant of concentrated egg
#2	Tolerant of concentrated egg OR egg IgE <2 kU/L and no history of clinical reactivity in previous 12 mo
#3	Tolerant of concentrated egg OR egg IgE <6 kU/L and no history of clinical reactivity in previous 12 mo

*Outcome definition used for all analyses unless noted.

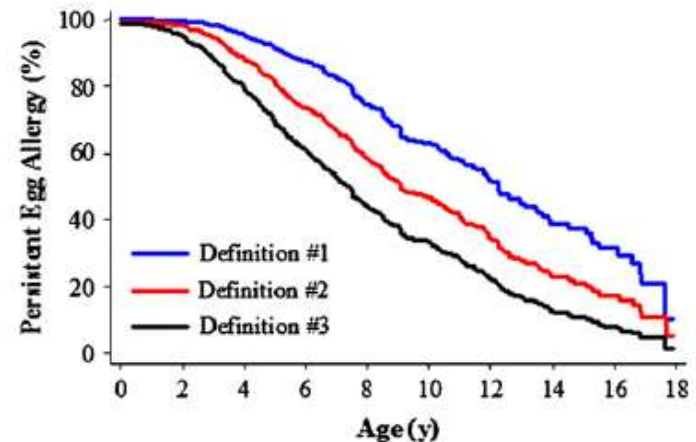


FIG 1. Egg allergy resolution over time. Graphs represent Kaplan-Meier survival curves for development of tolerance to egg over time using 3 definitions for tolerance.

The natural history of egg allergy

Fattori di rischio per la persistenza della allergia all'uovo sono lo sviluppo di asma e rinite allergica (poco la dermatite atopica) e la presenza di altre sensibilizzazioni allergiche, in specie per il grano e la soia

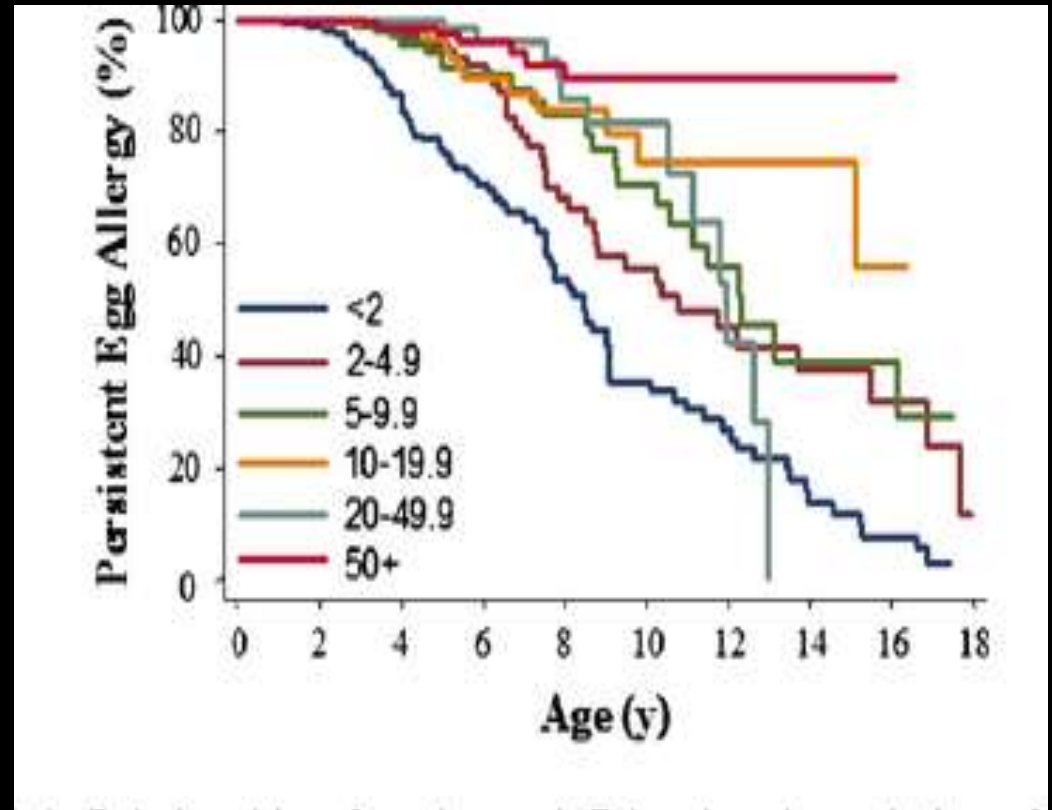
TABLE V. Clinical parameters and median time (y) to develop tolerance to egg

Characteristic	Presence (median years to develop egg tolerance)	Absence (median years to develop egg tolerance)	P value*
Other atopic disease			
Asthma	13.5	8.5	<.001
Allergic rhinitis	12.6	11.8	<.001
Eczema	12.3	11.1	.056
Other food allergies			
Peanut	12.6	11.1	<.05
Milk	12.6	11.4	<.05
Tree nut	13.1	11.4	<.01
Soy	13.9	11.4	<.005
Wheat	17.7	11.5	<.001
Sesame	13.5	11.9	<.01
Fish	15.2	11.9	<.05
Shellfish	13.9	12.0	.093

*Log-rank test.

The natural history of egg allergy

I bambini che raggiungono valori di IgE specifiche > 50 KU/l sono particolarmente a rischio di una allergia persistente



Cotto o crudo?

Immunologic changes in children with egg allergy ingesting extensively heated egg

Inizialmente arruolati 127 bambini (età media 6.9 anni). Dopo il TPO 27 erano allergici all'uovo cotto, 64 tolleravano l'uovo cotto in matrice di grano e 23 non allergici all'uovo. **Quindi 70% (64/91) dei bambini con allergia all'uovo tolleravano l'uovo cotto**

During each oral food challenge, a muffin and a waffle that each contained one third of an egg (approximately 2.2 g of egg protein) were ingested. The muffin was baked at 350F for 30 minutes in an oven, and the waffle (<0.625 inches thick to ensure thorough heating) was cooked in a waffle maker at approximately 500F for 3 minutes.

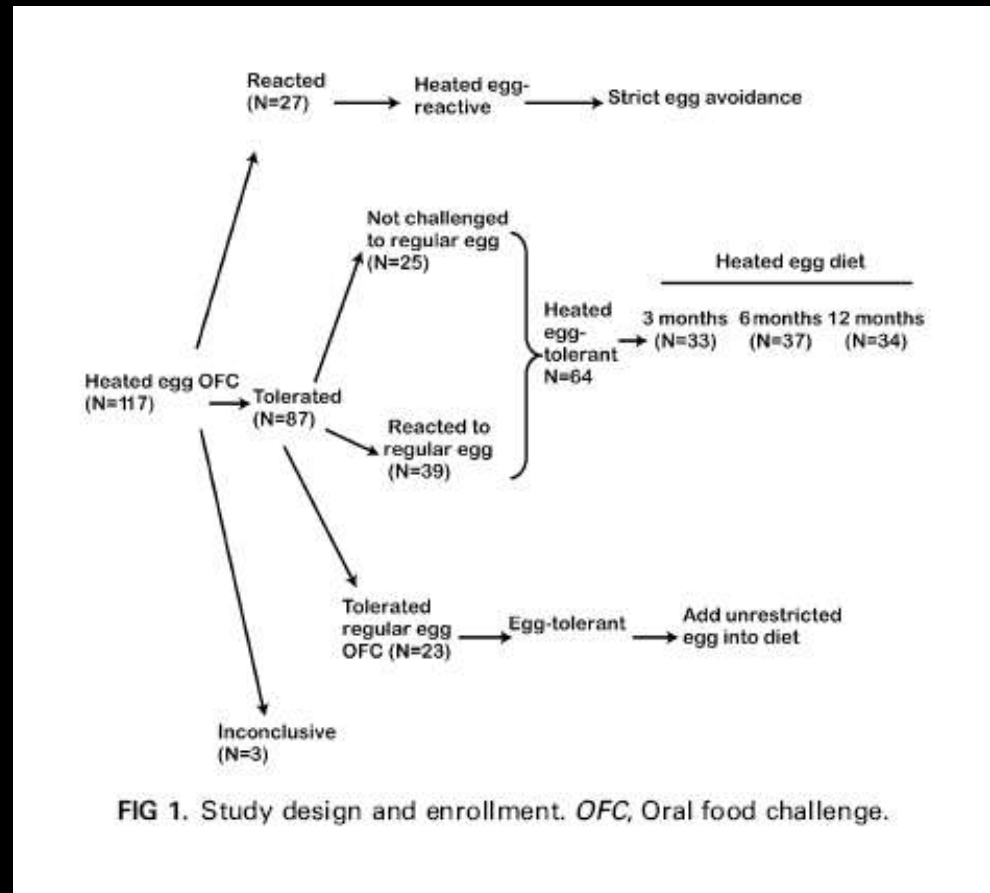


FIG 1. Study design and enrollment. OFC, Oral food challenge.

Immunologic changes in children with egg allergy ingesting extensively heated egg

Non vi era differenza nell'impiego di adrenalina negli allergici all'uovo crudo o cotto.

Coloro che ricevevano adrenalina avevano IgE specifiche per l'uovo (2.5 vs 0.7) e per l'ovomucoide (1.8 vs 0.5) più elevate degli altri e un rapporto IgE/IgG4 per ovomucoide più elevato.

Non c'era invece correlazione con la gravità della reazione

Le differenze comunque non erano tali da raggiungere un valore predittivo in grado di evitare il TPO

TABLE I. Challenge data clinical reactions

Parameter*	Extensively heated egg OFC (n = 27)	Scrambled egg/French toast (n = 39)
Symptoms		
Cutaneous	11	24
UA	19	27
LA	4	4
GI	11	18
CV	0	0
Treatment		
Epinephrine + other medications	5	9
Diphenhydramine only	14	23
Diphenhydramine + other medications (except epinephrine)	4	4
No treatment†	4	3
Eliciting dose (g) of egg protein, median (range)	2.0 (0.1-2.1)	1.5 (0.01-6)

OFC, Oral food challenge; *Cutaneous*, atopic dermatitis, urticaria, angioedema, rash, and pruritus; *UA*, upper airway (rhinorrhea, nasal congestion, sneezing, and oral pruritus); *LA*, lower airway (wheezing); *GI*, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain); *CV*, hypotension.

Numbers in each column represent the number of patients with specific symptoms on oral food challenge. Numbers in parentheses represent ranges.

*No statistical differences were observed between groups for any parameter.

†Subjects not treated with medications had transient allergic symptoms, including abdominal pain, a single episode of emesis, scattered urticaria, and oral pruritus.

25 bambini non hanno fatto il TPO con uovo crudo perché avevano le IgE specifiche > ai valori predittivi

Immunologic changes in children with egg allergy ingesting extensively heated egg

TABLE III. Follow-up immunologic parameters in children ingesting extensively heated egg

	Baseline	3 mo	P value	6 mo*	12 mo*
SPT (mm)	6 (5-8)	5 (3.4-7)	<.001	5 (3-7)	5 (3.5-6)
EW-specific IgE (kUA/L)	1.3 (0.6-4.3)	1.7 (0.6-5.2)	NS	1.7 (0.7-4.7)	1.3 (0.3-3.2)
OVA-specific IgE (kUA/L)	1.6 (0.7-4.7)	1.4 (0.5-4.9)	NS	1.6 (0.6-4.5)	1.1 (0.5-3.2)
OVM-specific IgE (kUA/L)	1.0 (0-3)	0.8 (0-3.3)	NS	1.2 (0.3-2.8)	1.0 (0.3-2.3)
OVA-specific IgG4 (µg/L)	0.4 (0-2)	4.6 (0.6-12.5)	<.001	3.1 (0.5-7.6)	3.1 (0.9-10)
OVM-specific IgG4 (µg/L)	0.1 (0-0.4)	0.6 (0.1-1.4)	<.001	0.5 (0.1-1.5)	0.6 (0.1-1.7)
OVA-specific IgE/IgG4 ratio	5.7 (1.7-81)	0.6 (0.1-2.9)	<.001	0.7 (0.1-2.9)	0.4 (0.03-0.5)
OVM-specific IgE/IgG4 ratio	7.4 (2-14.5)	1.1 (0.07- 3.3)	<.001	1.4 (0-6.7)	0.9 (0.2-4.2)

EW, Egg white; NS, not statistically significant ($P > .05$); OVA, ovalbumin; OVM, ovomucoid.

All numbers represent median values with 25% to 75% interquartile ranges provided in parentheses.

*No significant changes were noted in any of the parameters between the 3-, 6-, and 12-month follow-up intervals.

Nei bambini a dieta con uovo cotto in matrice di grano si assisteva ad una riduzione di alcuni parametri immunologici di sensibilizzazione allergica nei primi 3 mesi

Follow-up of the Heated Egg Clinical Trial

METHODS: HE-tolerant subjects incorporated HE into their diet and were periodically (every >6 months) challenged to less-heated-egg (LHE) in the form of egg noodles and meatballs, followed by RE. HE-reactive subjects were re-challenged to HE

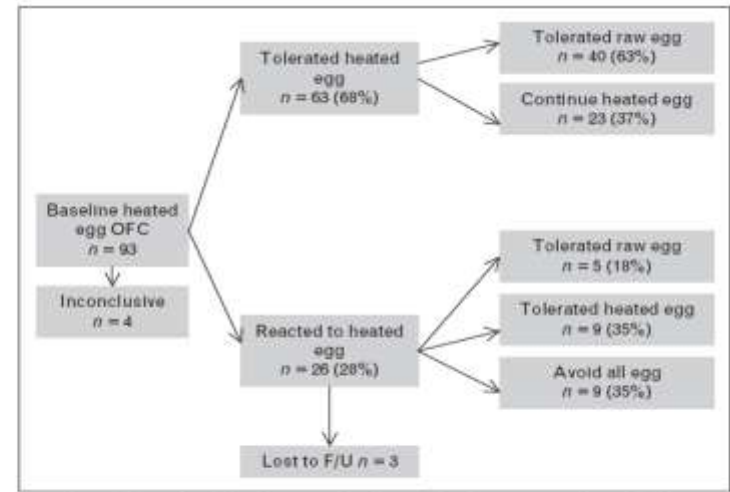


FIGURE 2. Study design and enrollment for baked egg trial. Adapted with permission from [29].

Patients who were initially baked egg tolerant were 3.3 times more likely to develop regular egg tolerance than those who were initially baked egg reactive. Patients in the active per-protocol group were 14.6 times more likely to develop regular egg tolerance than those in a retrospectively assessed comparison group who continued strict avoidance of egg and more likely to develop the tolerance earlier (median 22.0 versus 66.7 months; $P < 0.0001$). These findings suggest that the baked egg diet accelerates the development of regular egg tolerance when compared with strict avoidance.

Mechanisms underlying differential food allergy response to heated egg

La cottura

Denatura gli allergeni conformazionali

Aumenta l'effetto della digestione enzimatica
(sulla ovoalbumina)

Riduce la captazione intestinale (sia ovoalbumina che ovomucoide) e quindi la stimolazione dei basofili

L'Effetto Matrice

La cottura dell'uovo a 180° c per 10 minuti insieme al grano riduce la solubilità dell'ovomucoide. Lo stesso non avviene per la caseina.

L'immunoblotting suggerisce che l'ovomucoide formi dei polimeri e dei complessi ad alto peso molecolare aggregandosi con il glutine, cosa che rende meno solubile l'ovomucoide. Questo spiega perché sia necessario un cut off più elevato per le IgE specifiche per l'ovomucoide per predire la reattività all'uovo cotto in matrice di grano.

Kato Y, Watanabe H, Matsuda T. Ovomucoid rendered insoluble by heating with wheat gluten but not with milk casein. *Biosci Biotechnol Biochem* 2000;64: 198-201

Alimenti contenenti UOVO

Ben Cotto

Torte
Biscotti
Pasta all'uovo
Barrette al cioccolato
Hamburger

Cottura intermedia

Frittata
Homelette
Creme caramel
Creme Brullee
Meringhe

Crudo

Maionese
Sorbetto
Mousse con uovo
Gelati con uovo
Salsa tartara
freeze-dried egg proteins

allergenicità

Extensively heated milk and egg as oral immunotherapy

Food behavior under different heating conditions, as well as interactions with food matrix (e.g. as seen in the case of hen's egg white), are highly variable among different foods, and therefore, heating may not have similar effects for all foods. In addition, thermal processing may not simply alter IgE epitopes, as it can alter different biophysical and immunological properties of a food protein such as its structure, function, solubility, digestibility, and T-cell responses [22]. **Some food proteins are rendered more allergenic by thermal processing.** For peanut proteins, high temperature may enhance allergenicity as a result of glycation (Maillard reaction) that induces the formation of Ara h 2 aggregates that are more resistant to gastric digestion and bind IgE antibody more effectively than unheated Ara h 2

Dietary advice, dietary adherence and the acquisition of tolerance in egg-allergic children: a 5-yr follow-up

261 bambini con diagnosi di allergia all'uovo di cui
- 84 dopo TPO
- 131 per storia e SPT positivi
- 36 SPT positivi, mai assunto

Suggerimenti dietetici proposti

Dieta senza uovo
141 (84%)

Evitare anche le
tracce
65 (39%)

Possibile la assunzione
di alimenti contenenti
uovo cotto
43 (26%)

Aderenza ai
suggerimenti

113 (68%)

59 (35%)

33 (20%)

Dietary advice, dietary adherence and the acquisition of tolerance in egg-allergic children: a 5-yr follow-up

Il modo di seguire la dieta (stretta o non stretta) influenzava lo sviluppo di tolleranza

**Studio
retrospettivo**
Solo circa 1/3 dei bambini era stato sottoposto a TPO per l'uovo

Adherence	p-value*
0.77	
0.79	
0.81	
1.0	
0.45	
0.48	

A longitudinal study of resolution of allergy to well-cooked and uncooked egg

Method A longitudinal study of egg-allergic children from 2004 to 2010, who underwent challenge with well-cooked and if negative, uncooked egg. Participants underwent repeat annual challenges and egg-specific IgE measurement

Children with a history of a typical type-1 hypersensitivity reaction to egg and/or skin prick weal diameter $>3\text{mm}$ to whole egg extract **and/or** serum egg-white-specific IgE $>0.35\text{ kU/L}$ at the time of diagnosis were invited to participate. Subjects who had never eaten egg were enrolled if they had a positive challenge to egg and a positive SPT and/or serum-specific egg IgE

Challenges

Open challenges were either to well-cooked (sponge cake baked at 180°C for 20min), or uncooked egg (uncooked pasteurized frozen whole egg nuggets). Five incremental doses **of wellcooked** (0.4 g, 0.8 g, 1.5 g, 3 g, 6 g = **cumulative dose approximately 1.0 g protein**) or **uncooked egg** (0.5 g, 1 g, 2 g, 6 g, 12 g = **cumulative dose approximately 2.6 g protein**) were ingested at 10-min intervals

A longitudinal study of resolution of allergy to well-cooked and uncooked egg

If a subject had tolerated wellcooked egg previously then an uncooked egg challenge was undertaken on a separate day. All other subjects underwent a well-cooked egg challenge initially, and if they passed went on to an uncooked egg challenge.

Table 1a. Symptoms experienced during positive egg challenges (numbers of subjects are shown with percentages in parentheses). Symptoms are shown according to type of egg challenge

Type of egg challenge	Total positive challenges	Cutaneous	Gastrointestinal	Respiratory*	Rhinitis
Well cooked	28	18 (65)	19 (68)	0	11 (39)
Uncooked	61	46 (75)	34 (56)	9 (15)	20 (36)
Total	89	64	53	9	31

*Excluding rhinitis.

Cutaneous symptoms were recorded if erythema, urticaria or cutaneous angioedema occurred. Gastrointestinal symptoms were recorded if nausea, vomiting or abdominal pain (sufficient to alter behaviour) occurred and respiratory symptoms were recorded if wheezing or cough occurred during challenge.

La gran parte dei bambini hanno avuto solo reazioni lievi con l'uovo cotto (in matrice)

A longitudinal study of resolution of allergy to well-cooked and uncooked egg

The median age at which tolerance occurred was 67 months (5.6 years) for well-cooked and 127 months for uncooked egg.

(per tollerare l'uovo crudo si impiega il doppio del tempo)

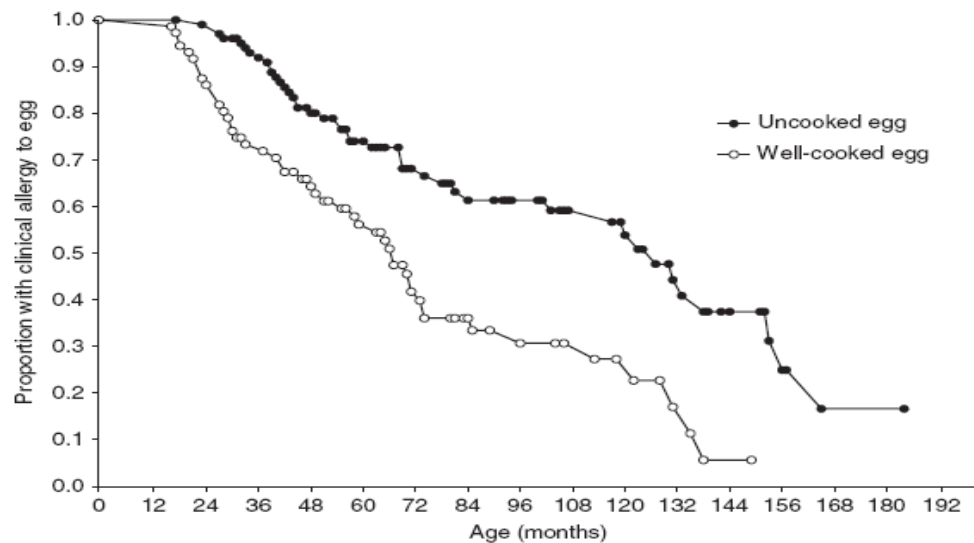


Fig. 1. Cumulative persistence (survival) of allergy to well-cooked and uncooked egg expressed using Kaplan-Meier survival curves. Log-rank test for difference between curves; $P < 0.0001$. Median age at acquisition of tolerance is 67 months (5.6 years) for well-cooked and 127 months (10.3 years) for uncooked egg.

I bambini che tollerano l'uovo cotto guariscono prima dalla allergia all'uovo.
La differente tolleranza si nota già dal secondo anno di vita

Clark A et al, *CI Exp Allergy* 2011; 41: 706-12

I Test Diagnostici

Premessa

PRICK TEST o “RAST”

Nelle varie casistiche della letteratura generalmente la loro positività (> 3 mm per i prick o 1 Classe per “RAST”)

Presenta:

“BUONA SENSIBILITÀ E
VALORE PREDITTIVO NEGATIVO”
(individuiamo la gran parte dei malati)

“BASSA SPECIFICITÀ E
VALORE PREDITTIVO POSITIVO”
(il test risulta spesso positivo nei soggetti sani)

Egg challenge in children with atopic dermatitis

Disegno: Studio prospettico che ha arruolato **107 bambini con dermatite atopica che non avevano mai ingerito l'uovo.**

Il TPO effettuato all'età mediana di 15 mesi è **risultato positivo in 72/107 (67,3%)**. Di questi 56/72 (77.8%) erano reazioni immediate, le restanti ritardate

Table 1. Albumen weal diameters and egg challenge outcome

Weal (mm)	Positive challenge (n)	Negative challenge (n)
0	4	26
1	2	3
2	3	1
3	18	2
4	32	3
5	4	0
6	3	0
7	2	0
8	2	0
9	0	0
10	2	0
Total	72	35

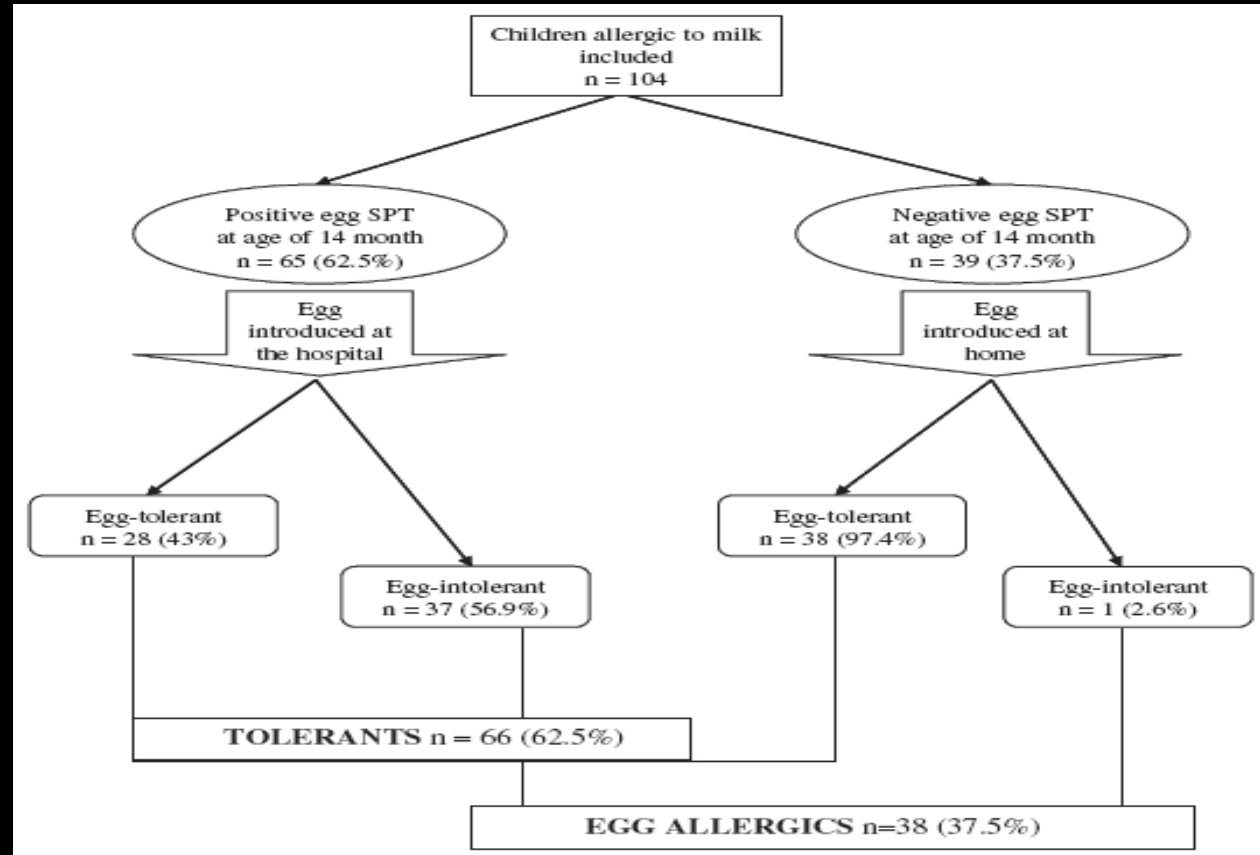
Uno SPT positivo **di 5 mm** presenta il 100% di specificità per un TPO positivo

Skin prick test predictive value on the outcome of a first known egg exposure in milk-allergic children

Children under the age of 1 yr who came consecutively to Allergy Department 2003–05, and were diagnosed with IgE mediated milk allergy were selected for this study. Egg introduction was completely avoided until the age of 14 months when clinical history, skin prick tests (SPT), specific-IgE antibodies determination and egg challenge test were performed

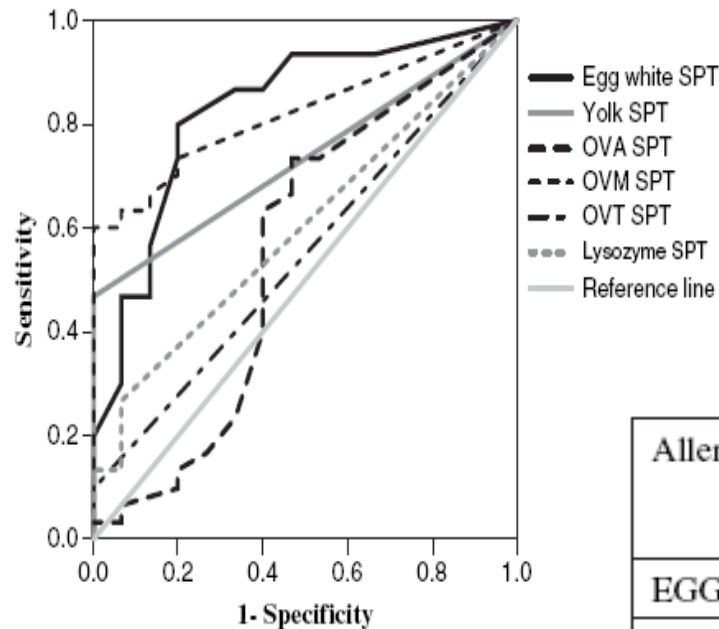
Skin prick test predictive value on the outcome of a first known egg exposure in milk-allergic children

One hundred and four patients were included in the cohort, 31 (30.4%) had at least one atopic parent, 60 (59.4%) had atopic dermatitis 17 (16.3%) had asthma and 52 (50%) had positive prick test to other tested foods (fish, nuts, apple, peach, melon or lentils).



Gl allergici all'uovo hanno più frequentemente la dermatite atopica e multiple sensibilizzazioni ad alimenti

Skin prick test predictive value on the outcome of a first known egg exposure in milk-allergic children



Il bianco dell'uovo e l'ovomucoide presentano la migliore area sotto la curva. Il bianco dell'uovo la migliore sensibilità e l'ovomucoide la migliore specificità

Il Cut-off ottimale (che combina la migliore sensibilità e specificità) è 6 mm per l'albume e 5 mm per l'ovomucoide

Allergen	Area under the curve (95% confidence interval)	Optimal decision point (mm)
EGG WHITE	0.83 (0.70–0.96)	6 mm
YOLK	0.73 (0.59–0.88)	3 mm
OVA	0.55 (0.36–0.75)	3 mm
OVM	0.82 (0.70–0.94)	5 mm
OVT	0.55 (0.37–0.72)	
LISOZIME	0.60 (0.43–0.96)	

Livelli di IgE specifiche (Cap System) proposti come Cut off diagnostici per l'uovo e relativo potere predittivo positivo

Autore	n.	Età	DA (%)	Allergia all'uovo (%) (preval)	Cut off PPV 90%	Cut off PPV 95%	Cut off PPV 99%	Metodo
Sampson 1997	196	5.2 anni (media)	100	73	2	6	nd	ROC
Sampson 2001	100	3.8 anni (mediana)	60	80	nd	7	nd	ROC
Boyano Martinez 2001	81	16 mesi (media)	43	79	nd	0,35*		ROC
Osterballe 2003	56	2,3 anni (mediana)	100	64			1,5^	ROC
Celik-Bilgili 2005	992	13 mesi (mediana) †	88	30	6,3 ‡	12,6	59,2	RL
Mehl 2006	437	13 mesi (mediana)	90	29	nd	15,9	75,5	RL
Kamata 2007	764	1.3 anni (mediana)	74	49	nd	25.5	nd	RL

Calvani M, Zappala D, Panetta V, Prospettive in pediatria 2007; 37: 165-72

The predictive value of skin prick testing for challenge-proven food allergy: A systematic review

Table 1. Published skin prick test (SPT) cutoffs in egg allergic children, stratified by age (<2 and ≥2 yrs)

Study	Sample size	Population	Outcome	Median age (range)	Allergy prevalence (%)	Method	SPT cutoff (mm)
Boyano Martinez (12)	81	Children with history of egg allergy or suspected egg allergy	64 positive OFC*	Under 2 yrs	79	93% PPV ROC curves	3
Monti (7)	107	Children with atopic dermatitis who had never ingested egg	72 positive OFCs	5 months (1–19 months)	67	94% PPV	4
Sporik (13)	39	Children referred to allergy clinic with suspected food allergy or retested after positive challenge at least 12 months prior	29 positive OFC (subgroup of below)	Under 2 yrs	74	100% specificity ROC curves	5
Tripodi (15)	47	Children attending allergy clinic with suspected egg allergy (39) or recent positive OFC to egg (8)	20 positive OFC	Mean 6.2 yr (1.1–15.7 yr)	43	100% PPV ROC curves 2 × 2 tables	6
Sporik (13)	121	Children referred to allergy clinic with suspected food allergy or retested after positive challenge at least 12 months prior	93 positive OFC	36 months (1–154 months)	77	100% specificity ROC curves	7
Dieguez (8)	157	Children previously diagnosed egg allergic, examining persistence of allergy	100 positive DBPCFC	2.5 yr (15 months–16 yr)	63	95% PPV ROC curves	9
Verstege (14)	160	Children referred to hospital with suspected food allergy (SPT fresh food allergens)	101 positive OFC (75% DBPCFC and 25% open OFC)	22 months (3 months–14.5 yr)	63	95% PPV Logistic regression	13
Mehl (9)	193	Children with suspected food allergy	128 positive OFC	13 months (3 months–14 yr)	66	95% PPV Logistic regression	14

*OFC was not conducted, but considered positive, in children who had history of anaphylaxis or history of multiple episodes of urticaria and angioedema within 2 h of egg ingestion and last episode within 3 months of doctors visit and positive SPT (n = 7). OFC, oral food challenge; PPV, positive predictive value.

ImmunoCAP

<u>Code</u>	<u>Name</u>	<u>Latin name</u>
<u>f76</u>	<u>nBos d 4 α-lactalbumin</u>	<u>Bos taurus</u>
<u>f77</u>	<u>nBos d 5 β-lactoglobulin</u>	<u>Bos taurus</u>
<u>e204</u>	<u>nBos d 6 γ-globulin</u>	<u>Bos taurus</u>
<u>f78</u>	<u>nBos d 8 α-casein</u>	<u>Bos taurus</u>
<u>f334</u>	<u>nBos d Lactalbumin</u>	<u>Bos taurus</u>
<u>f233</u>	<u>nGal d 1 Ovalbumin</u>	<u>Gallus domesticus</u>
<u>f232</u>	<u>nGal d 2 Ovalbumin</u>	<u>Gallus domesticus</u>
<u>f323</u>	<u>nGal d 3 Conalbumin</u>	<u>Gallus domesticus</u>
<u>f355</u>	<u>rCyp c 1 Carpomyosin</u>	<u>Cyprinus carpio</u>
<u>f426</u>	<u>rGad c 1, Crustacean</u>	<u>Gadus morhua</u>
<u>f351</u>	<u>rPen a 1 Tropomyosin, Shrimp</u>	<u>Penaeus aztecus</u>

Con l'immunoCap è oggi possibile la diagnostica molecolare solo nei confronti di 3 molecole dell'uovo

ISAC: Ricerca 112 molecole allergeniche contenute in 51 sostanze

ALLERGEN COMPONENTS BY SOURCE

Mentre con l'ISAC è possibile ricercare 4 molecole dell'uovo (il Gal d1, Gal d2, il Gal d3 e il Gal d5)



Clinical usefulness of microarray-based IgE detection in children with suspected food allergy

Background:.. The aim of this study was to evaluate the utility of microarray-based IgE detection in the diagnostic workup of food allergy and to compare this new diagnostic tool with established methods of allergen-specific IgE detection.

Methods: We investigated 130 infants and children with suspected allergy to cows milk (CM) or hens egg (HE). Serum IgE measurements, skin prick tests, allergen microarray assays and controlled oral food challenges with HE and CM were performed. **During 145 oral provocations, oral application of HE induced clinical symptoms in 45 out of 60 individuals (75%). (uovo crudo)**

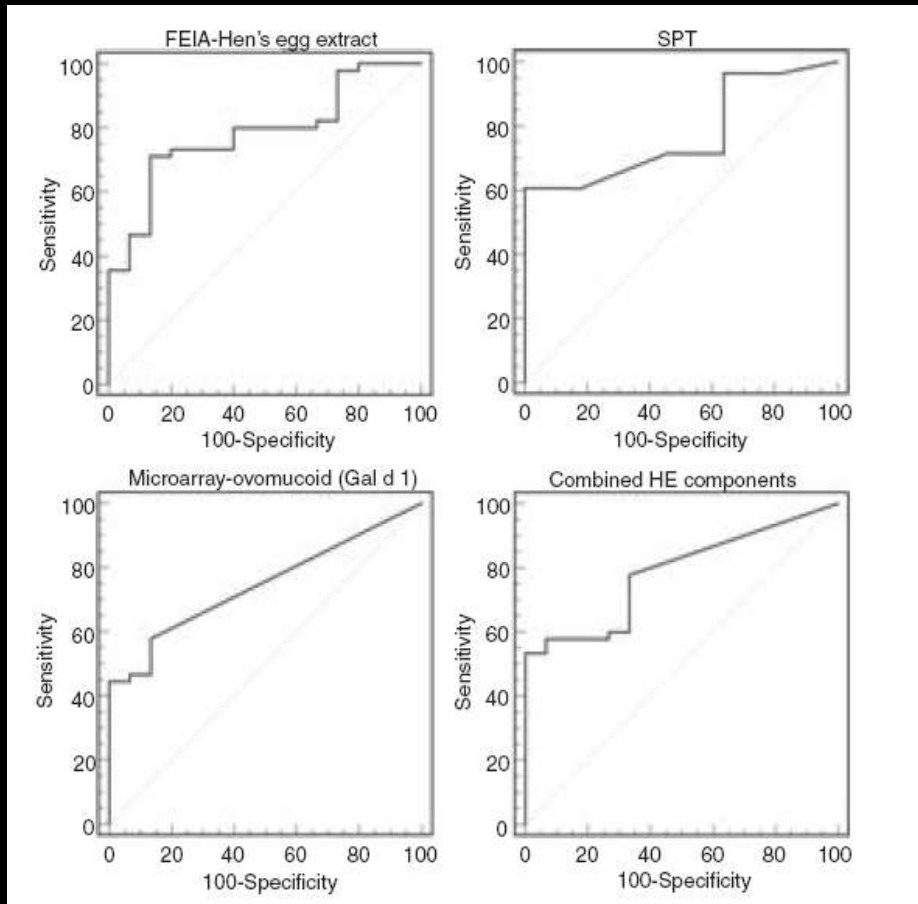
Table 1. Patient characteristics and description of reaction types during oral food challenge

	Median (range)	<i>n</i>	%
Age at oral food challenge (months)	14 (5–150)		
Atopic eczema		124	95
Gender			
Male		70	54
Female		60	46
Open oral food challenges		42	29
DBPCFC		103	71
Suspected CM allergy		85	59
Total serum IgE (kU/l)	213.5 (3.5–12085)		
CM specific IgE (kU/l)	2.81 (0.36–87.2)		
Suspected HE allergy		60	41
Total serum IgE (kU/l)	159.0 (6.0–3920)		
HE specific IgE (kU/l)	4.08 (0.37–57.2)		
Symptoms elicited by provocation			
Urticaria		51	35
Flushing		47	32
Pruritus		30	21
Angioedema		2	1.4
Exacerbation of AE		12	8
Vomiting		23	16
Diarrhea		12	8
Stridor		2	1.4

Clinical usefulness of microarray-based IgE detection in children with suspected food allergy

Comparison of FEIA results with each single microarray component by nonparametric Wilcoxon testing revealed no statistically significant differences between AUC values... One single allergen component i.e. Gal d 1 generated similar AUC results as the respective microarray component combination or FEIA testing **while highest AUC values were obtained by SPT with native HE preparations.**

The combination of all allergen microarray results generated the same or highly similar AUC values as compared to FEIA testing in HE allergy diagnosis.



Clinical usefulness of microarray-based IgE detection in children with suspected food allergy

Table 3. Summary of clinically relevant assay performance parameters of allergen microarrays, fluorescence enzyme immunoassays and skin prick tests in the diagnosis of HE allergy

Allergen Microarray					FEIA	SPT
Allergen	Gal d 1	Gal d 2	Gal d 4	Combination*	HE extract	Native HE
Cut Off	> 0	> 0	> 0	0.2	2.9	9.0
AUC [†]	0.8 (0.6–0.9)	0.77 (0.6–0.8)	0.6 (0.5–0.7)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.6–0.9)
Sensitivity (%)	57.8 (42.2–72.3)	57.8 (42.2–72.3)	17.8 (8.0–32.1)	53.3 (37.9–68.3)	71.1 (55.7–83.6)	60.7 (40.6–78.5)
Specificity (%)	86.7 (59.5–98.0)	80 (51.9–95.4)	100 (100)	100 (100)	86.7 (59.5–98.0)	100.0 (71.3–100.0)
PPV (%)	92.9	89.7	100	100	94	100.0
NPV (%)	40.6	38.7	28.8	41.7	50	50.0
P-value [‡]	0.61	0.2	0.044	0.98	–	–

*Combination of all fluorescence intensity values of single HE allergen components.

[†]Allergen microarray (FI), FEIA (kU/l) and SPT (wheal diameter) results with 95 % confidence intervals corresponding to the highest accuracy value obtained by prior ROC analysis.

[‡]P-values of non-parametric paired Wilcoxon tests FEIA and allergen microarray with respect to AUC values.

In conclusion, allergen microarrays provide a new tool to diagnose symptomatic CM and HE allergy. They show performance characteristics comparable to the current diagnostic tests and may be indicated in small children in whom only small blood volumes are obtainable. However, they are not capable of replacing double-blind, placebo-controlled food challenges in most cases.

Ott H et al, *Allergy* 2008; 63: 1521-8

Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy

Background: Children with allergy to raw egg white might tolerate low amounts of heated egg. Ovomucoid-specific IgE antibodies have been suggested to be predictors of whether children could tolerate heat-treated egg.

Methods: One hundred eight patients (median age, 34.5 months) with suspected egg allergy underwent double-blind, placebocontrolled food challenges with raw and heated egg. The outcomes of the challenges were related to the serum concentration of specific IgE antibodies and total IgE by using ImmunoCAP.

Subjects Patients (male/female ratio, 67/41) had mostly atopic dermatitis, asthma, and, in a few cases, gastrointestinal symptoms and anaphylaxis. The patients were divided into 3 groups on the basis of their immediate reactions to oral provocation tests.

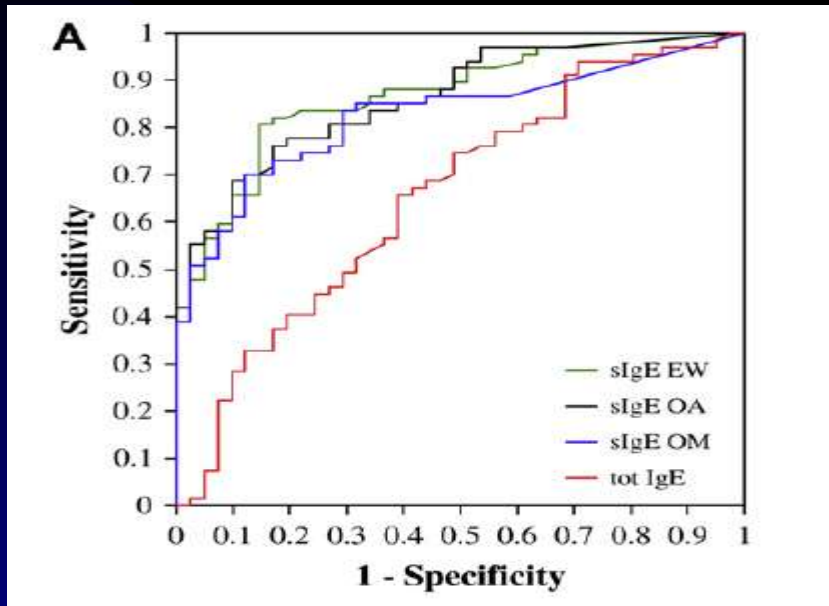
Group A (n 38) had positive challenge results for heated egg white (the subjects were considered reactive to both heated and raw egg white) ,(Allergici all'uovo cotto e crudo)

Group B (n 29) consisted of subjects who had positive reactions to raw egg white but negative reactions to heated egg white, and (allergici all'uovo crudo ma non cotto)

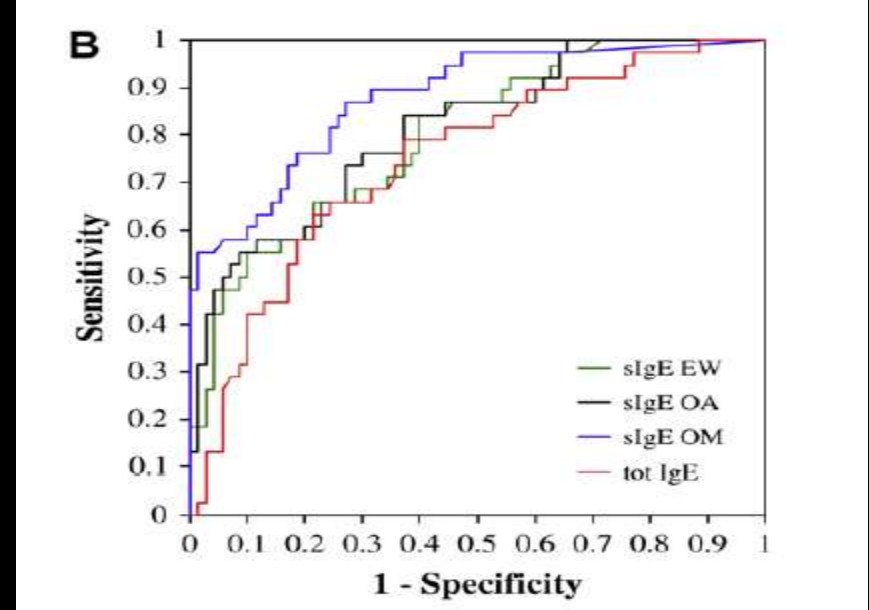
Group C (n 41) consisted of subjects who had negative responses to both raw and heated egg white. (non allergici all'uovo)

Uovo cotto: bollito 60 minuti a 90°

Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy



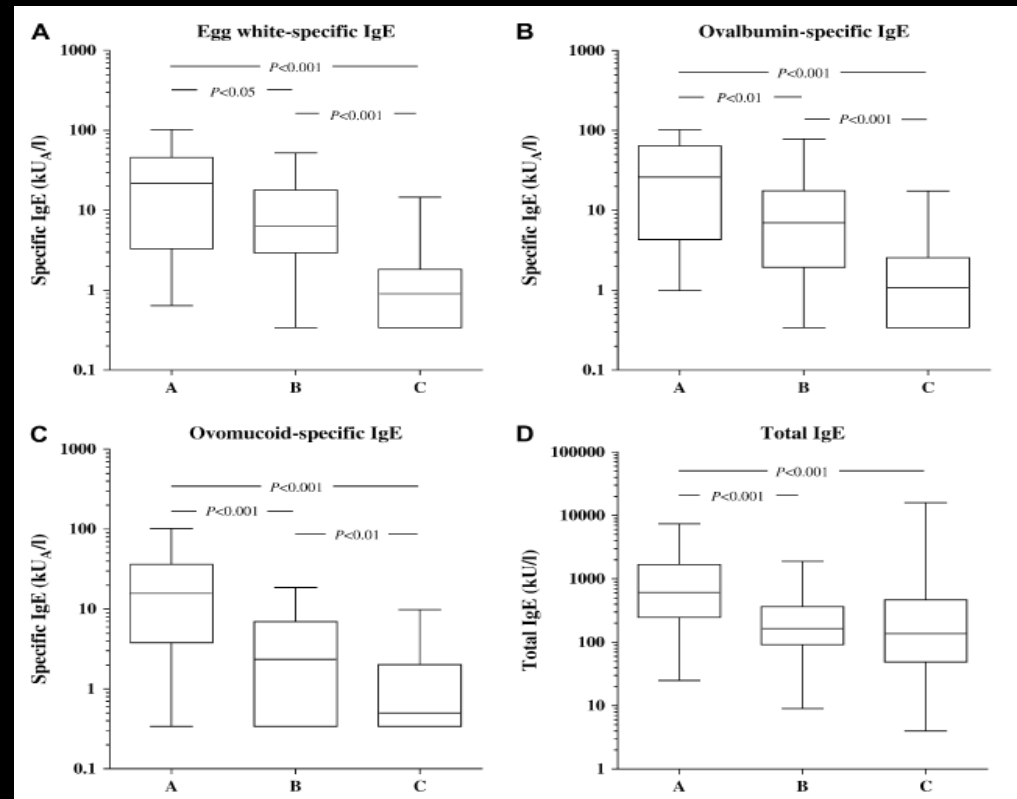
Le Ige specifiche per il bianco di uovo riescono meglio di quelle per la ovoalbumina e l'ovomucoide a differenziare i pazienti allergici all'uovo crudo rispetto ai tolleranti.



Le IgE specifiche per l'ovomucoide differenziano meglio gli allergici all'uovo cotto rispetto ai tolleranti. Il Cut off ottimale è 4.40 kUA/L, che corrisponde ad una sensibilità del 76% e a una specificità dell'81%.

Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy

DISCUSSION: This study demonstrates that quantitative measurements of specific IgE antibodies, both toward egg white and ovomucoid, are useful in the management of children with egg allergy. Specific IgE antibody levels to egg greater than 7 kUA/L were highly indicative of allergy toward raw egg, whereas specific IgE antibodies to ovomucoid greater than 11 kUA/L were indicative for allergy toward heated egg white.



Questi “decision point” sono stati individuati con il livello delle IgE che rappresenta il 95% della specificità del test, valore che non dipende dalla prevalenza della malattia nella popolazione

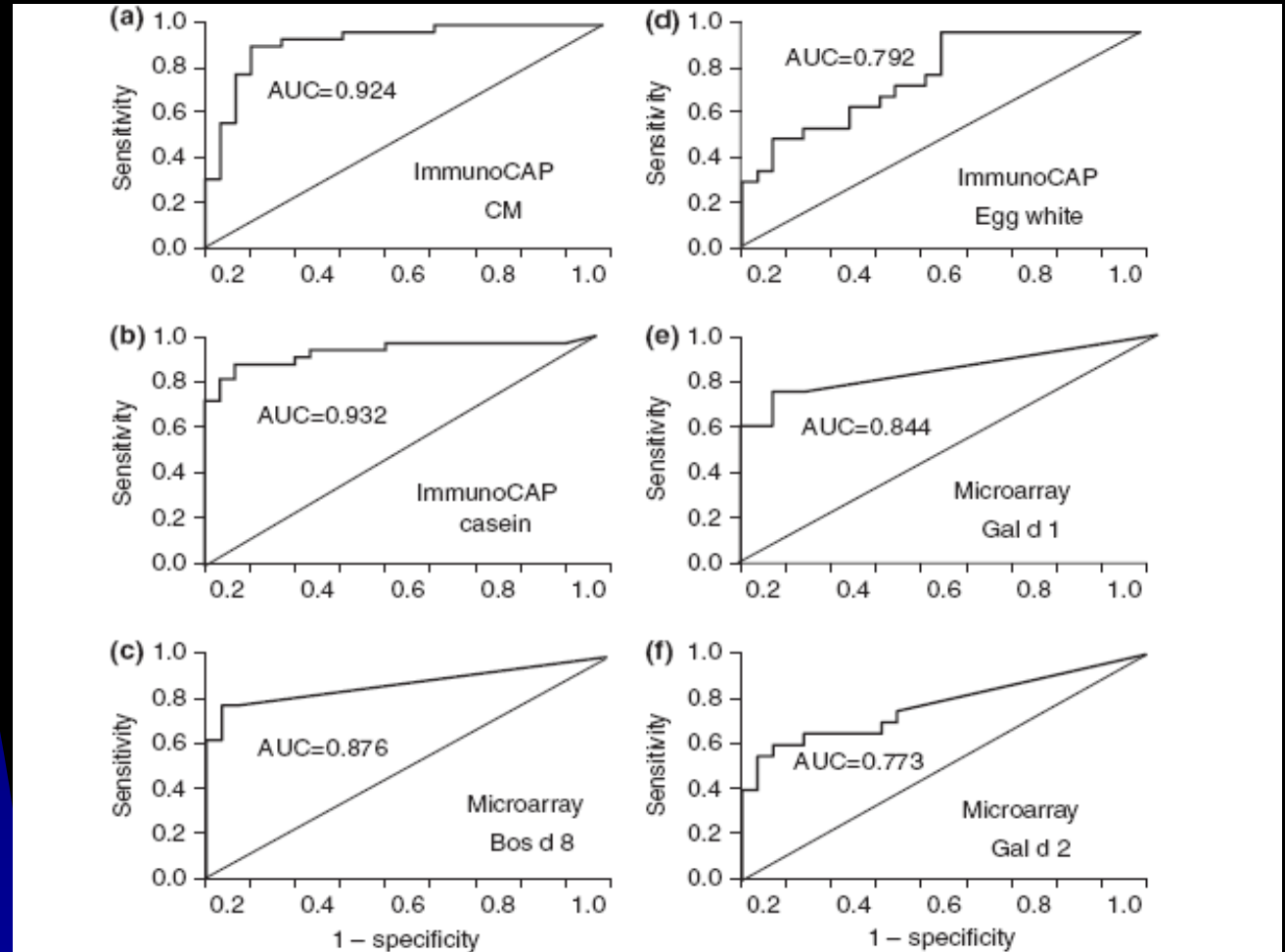
Performance of a component-based allergen-microarray in the diagnosis of cow's milk and hen's egg allergy

Methods. One-hundred and four children with suspected IgE-mediated hypersensitivity to CM or HE were studied. In all patients, skin prick test, ImmunoCAP, microarray and FCT were performed. **The FCT material was cooked egg (boiled for 10 min) or raw egg in the case of negative FCT to cooked egg.**

Results The microarray components Gal d 1 (20/46 patients) and Gal d 2 (24/46) for HE were the most frequently recognized allergens. Using the FCT results as the reference parameter, sIgE to Gal d 1 had the highest area under the curves. These were not significantly different from those obtained using the ImmunoCAP. Use of 95% clinical decision points (CDP) **for sIgE to Gal d 1** resulted in higher negative predictive values (79%) than those obtained with the ImmunoCAP (59%).

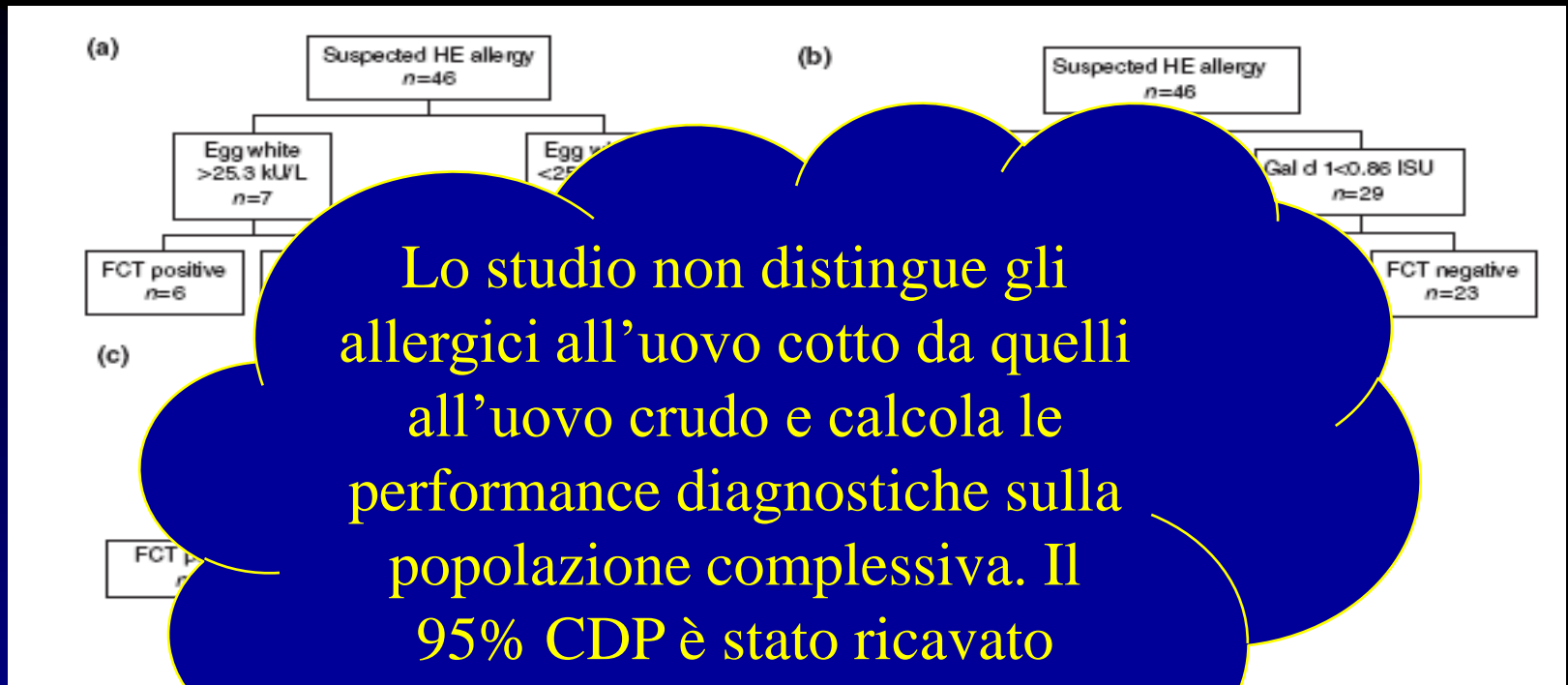
Performance of a component-based allergen-microarray in the diagnosis of cow's milk and hen's egg allergy

il Gal d1 ha la migliore area sotto la curva. La prestazione è lievemente superiore al semplice CAP per l'uovo.



Receiver operator characteristic curves for cow's milk (CM) ImmunoCAP extracts [(a) CM] [(b) casein] and for the allergen

Performance of a component-based allergen-microarray in the diagnosis of cow's milk and hen's egg allergy



In suspected HE allergy, using sIgE levels to Gal d 1, with the 95% CDP for sIgE to egg white, measured with ImmunoCAP, would have eliminated the need of the FCT in approximately 15%, the use of 95% CDP for Gal d 1 sIgE would have led to a 37% reduction, and to a reduction in positive FCT (6 vs. 16).

Ovomucoid (Gal d 1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation

Study population

The studied population was represented by 68 children (47 male, 69.1%), age ranging from 1 to 11 years (median 4.1 years), referring to our centre by the family paediatricians for suspected HE allergy. **Patients underwent double-blind, placebo-controlled food challenge with boiled and raw eggs.**

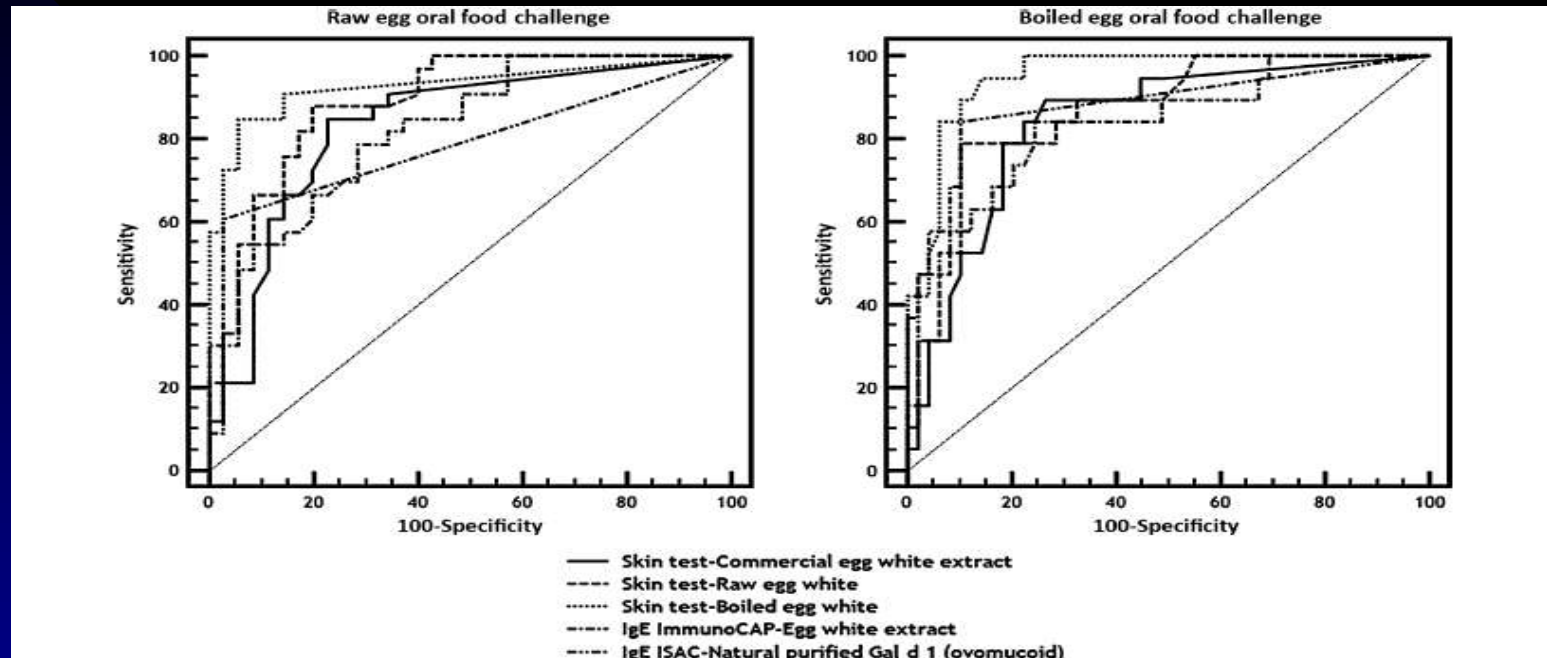
Popolazione "poco allergica":
ben 35/68 era SPT negativi
per l'uovo

Uovo sodo (cotto 10 minuti a 100°)

Table 1. Group characteristics and allergic symptoms recorded after hen's egg double-blind placebo-controlled challenges

	Hen's egg reactivity Groups*		
	A	PT	ST
Number of subjects			
Subjects	19	14	35
Male/Female	15/4	9/5	23/12
DBPCFC			
Raw Egg Reactive	Yes	Yes	No
Boiled egg reactive	Yes	No	No
Median age	4.33	3.17	4.42
Atopic dermatitis	16	5	8
Diagnostic tests^o			
CAP (IU/L)			
Total IgE	285	134	152
SPT (mm ²)			
Raw egg white	80	62.4	0
Boiled egg white	50.3	18	0
Egg white commercial	24.5	10.5	0
Raw egg yolk	17	24	0
Boiled egg yolk	1	0	0
Egg yolk commercial	11.8	7	0
CAP (kU _a /L)			
Egg white	7.75	1.82	0.45
Egg yolk	1.64	0	0

Ovomucoid (Gal d 1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation



The best performance on the analysed ROC curve, using as gold standard the raw and boiled egg DBPCFC, was provided by the boiled white SPT (Fig. 1), with a criterion set at $>11.6 \text{ mm}^2$.

Ovomucoid (Gal d 1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation

Table 2. Overall test performance results as obtained by receiver operating characteristic analysis comparing all diagnostic tests performed in the study and using raw and boiled hen's egg double-blind placebo-controlled food challenge (DBPCFC) as gold standards

Gold standard	Test	Allergen preparations	Optimal cut-off point	Sensitivity (%)	Sensitivity 95% CI	Specificity (%)	Specificity 95% CI	+LR	-LR	PPV (%)	NPV (%)	
Boiled egg	SPT (mm ²)	Egg white extract	8	84	67.2-94.7	77	59.9-89.6	4	0.2	77	84	
		Raw egg white	48	88	71.8-96.6	80	63.1-91.6	4	0	81	88	
		Boiled egg white	11.6	85	68.1-94.9	94	80.8-99.3	15	0.2	93	87	
		Egg yolk extract	0	70	51.3-84.4	83	66.4-93.4	4	0.3	79	74	
		Raw egg yolk	8.4	79	61.1-91	80	63.1-91.6	4	0.3	79	80	
	CAP (kUa/L)	Boiled egg yolk	4.3	45	28.1-63.6	94	80.8-99.3	8	0.6	88	65	
		Egg white	1.23	79	61.1-91.0	71	53.7-85.4	3	0.3	72	78	
		Egg yolk	0.11	64	45.1-79.6	88	72.5-96.7	5	0.4	84	71	
		ISAC (kUa/L)	Gal d 1	0	61	42.1-77.1	97	85.1-99.9	21	0.4	95	72
			Gal d 2	0.21	40	22.9-57.9	94	80.8-99.3	7	0.6	87	62
	Gal d 3		0.06	18	7.0-35.5	100	90-100		0.82	100	57	
	Raw egg	SPT (mm ²)	Gal d 5	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Egg white extract	11	89	66.9-98.7	73	58.9-85.1	3	0.1	57	95
			Raw egg white	71.2	79	54.4-93.9	90	77.8-96.6	8	0.2	75	91
			Boiled egg white	23.3	95	74.0-99.9	86	72.8-94.1	7	0	72	98
Egg yolk extract			10.7	58	33.5-79.7	86	72.8-94.1	4	0.4	61	84	
CAP (kUa/L)		Raw egg yolk	8.4	68	43.4-87.4	59	44.2-73	2	0.5	39	66	
		Boiled egg yolk	4	53	28.9-75.6	86	72.8-94.1	4	0.5	59	82	
		Egg white	2.25	84	60.4-96.6	75	61.1-86.7	3	0.21	57	92	
		Egg yolk	0.11	84	60.4-96.6	81	67.4-91.1	4	0.19	64	92	
		ISAC (kUa/L)	Gal d 1	0	84	60.4-96.6	90	80.4-97.7	8	0.18	76	94
Gal d 2			0	53	28.9-75.6	84	70.3-92.7	3	0.51	57	82	
Gal d 3			0.41	21	6.1-45.6	98	89.1-99.7	10	0.81	80	76	
Gal d 4			0.06	18	7.0-35.5	100	90-100		0.82	100	57	
Gal d 5			NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

CAP, IgE detection using ImmunoCAP system (Phadia, Sweden); CI, Confidence interval; ISAC, IgE detection using ISAC 103 microarray system (PMD, Austria); +LR, positive likelihood ratio; -LR, negative likelihood ratio; NA, not assessed; NPV, negative predictive value; PPV, positive predictive value; SPT, skin prick test.

Lo SPT per uovo cotto e il Gal D1 presentano il miglior rapporto di verosimiglianza per la diagnosi di allergia all'uovo cotto

Il Test di Provocazione Orale

Caratteristiche dei test di provocazione orale per alimenti in Italia. Studio retrospettivo multicentrico

783 TPO effettuati in 6 centri italiani

Tab. II. Alimenti testati nei TPO nei diversi centri.

Centri	Uovo	Latte	Frumento	Banana	Manzo	Arachide	Pollo	Nocciola	Noce	Kivi
1	22 (34,4)	29 (45,3)	0	0	3 (4,7)	0	3 (4,7)	0	0	0
2	35 (47,3)	33 (44,6)	6 (8,1)	0	0	0	0	0	0	0
3	64 (63,4)	31 (30,7)	0	0	1 (0,7)	0	1 (0,7)	0	0	0
4	14 (23)	45 (73,8)	0	0	0	0	0	0	0	0
5	18 (24,3)	50 (67,6)	1 (1,4)	0	0	0	0	0	0	0
6	170 (41,6)	110 (26,9)	27 (6,6)	12	6 (1,5)	10 (1,2)	6 (1,5)	9 (2,2)	8 (2,0)	7 (1,7)
Totale	323 (41,3)	298 (38,1)	34 (4,1)	12 (1,5)	10 (1,2)	10 (1,2)	10 (1,2)	9 (1,1)	8 (1,0)	7 (0,8)

Oral food challenges in children are safe and severe reactions are almost all due to respiratory symptoms.

Methods. A retrospective charts review was performed in children who underwent food challenges in 3 Allergy Clinics in Italy.... Children were referred to the Clinics primarily because they had a positive history of reactions to food and/or detectable specific IgE. Children already diagnosed as allergic and re-challenged to test the persistence of the allergy were also included.

Table 1 Demographics and challenge details of all OFCs

	All N = 526	Positive challenges N = 254 (48.3%)	Negative Challenges N = 272 (51.7%)	P value
Age (yr) median (interquartile range)	4 (2 – 6)	4 (2 – 6)	4 (2 – 7)	0.6
Male sex	353	170 (48.2)	183 (51.8)	0.9
DBPCFC	75	37 (49.3)	38 (50.7)	0.8
SPT +ve for food (%)	337 (64.1)	209 (89.7)	128 (54.7)	< 0.001
<i>Foods</i>				
Egg	218	123 (56.4)	95 (43.6)	0.002*
Milk	167	83 (49.7)	84 (50.3)	0.6 *
Wheat	33	15 (45.5)	18 (54.5)	0.7 *
Other foods	108	33 (30.6)	75 (69.4)	< 0.001*

* Statistical difference is assessed between the positive and negative challenges to the food in question and all other foods.

Oral food challenges in children are safe and severe reactions are almost all due to respiratory symptoms.

There were 254 (48.3%) positive OFCs out of a total of 526 challenges. OFCs with egg were more commonly positive than OFCs to all other foods combined ($p = 0.002$).

Egg challenges were conducted mainly with raw egg (192/218; 88%) but also with heated egg (26/218; 12%).

Within egg challenges, challenges with raw egg were more commonly positive (116/192; 60.4%) than with heated egg (7/26; 26.9%) ($P = 0.001$).

Anaphylactic reactions to raw eggs after negative challenges with cooked eggs

These reports and our observations raise several questions of importance to the clinician. Should we do follow-up challenges for egg hypersensitivity with raw eggs exclusively? On the other hand, should we continue to challenge with cooked eggs? More studies will be necessary to answer these questions. In the meanwhile, we suggest mixing freeze-dried egg with oatmeal or with any other food tolerated by the patient. If the patient does not become tolerant in a “reasonable” follow-up time period, we would recommend testing cooked eggs to allow a diversification of the diet.



Grazie per l'attenzione e..
Arrivederci a Diari ver 2.012
(25-27 ottobre 2012, Roma)

Diari ver. 2.012

Nessun dorma



Roma, 25-27 Ottobre 2012

Chicken serum albumin (Gal d 5*) is a partially heat-labile inhalant and food allergen implicated in the bird-egg syndrome

ImmunoCAP ISAC® Allergen Components

Allergen component	Allergen source COMMON NAME	LATIN NAME	PROTEIN GROUP
nGal d 1	Egg, Ovomuroid	<i>Gallus domesticus</i>	
nGal d 2	Egg, Ovalbumin	<i>Gallus domesticus</i>	
nGal d 3	Egg, Conalbumin	<i>Gallus domesticus</i>	
nGal d 5	CSA (Livetin)	<i>Gallus domesticus</i>	Serum albumin
rCvp c 1	Carp	<i>Cyprinus carpio</i>	Parvalbumin

HDM: house-dust mites; Neg.: negative.

Table 3. Results of bronchial provocation tests (BPT) to methacholine and CSA

Patients	Methacholine inhalation test PC ₂₀ (mg/ml)	BPT to CSA Maximum fall in FEV ₁ from baseline (%)	BPT to CSA PC ₂₀ allergen (mg/ml)
1	> 16	25	0.008
2	0.20	26	0.034
5	> 16	21	0.009
6	0.90	25	0.012
7	ND	28	0.003
8	0.13	23	0.015
2 control subjects	—	Neg.	—

ND: not done.

Il test di provocazione bronchiale con alfa-livetina causava la rapida insorgenza di una crisi asmatica in tutti i soggetti che soffrivano di asma.

Quirce S et al, Allergy 2001; 56: 754-62

Fattori clinici e di laboratorio che sono stati associati allo sviluppo di tolleranza per l'uovo sono

Sintomi lievi alla ingestione

Ford RP et al Arch Dis Child 1982

Ridotte dimensioni degli SPT

Boyano-Martinez T J Allergy Clin Immunol 2002

Ridotti livelli di IgE specifiche

Dannaeus A Clin Allergy 1981

Precoce età alla diagnosi

Shek LP, J Allergy Clin Immunol 2004

Percentuale di riduzione nel tempo delle IgE specifiche

Shek LP, J Allergy Clin Immunol 2004

Oral Food Challenges in Children with a Diagnosis of Food Allergy

Table II. OFC results on foods avoided due to immunoassay or PST

Food group	Avoiding on admission	OFC positive result	OFC negative result	Avoiding on discharge	% Negative
Egg	10	1	9	1	90%
Fruits	10	2*	8	2	80%
Meats	13	0	13	0	100%
Milk	9	0	9	0	100%
Oats	4	0	4	0	100%
Peanut	7	1	6	1	86%
Shellfish	2	0	2	0	100%
Soy	19	1	18	1	95%
Vegetables	6	0	6	0	100%
Wheat	13	3	10	3	77%
Other	18	0	18	0	100%
Totals	111	8	103	8	93%

*Two positive tests to banana.

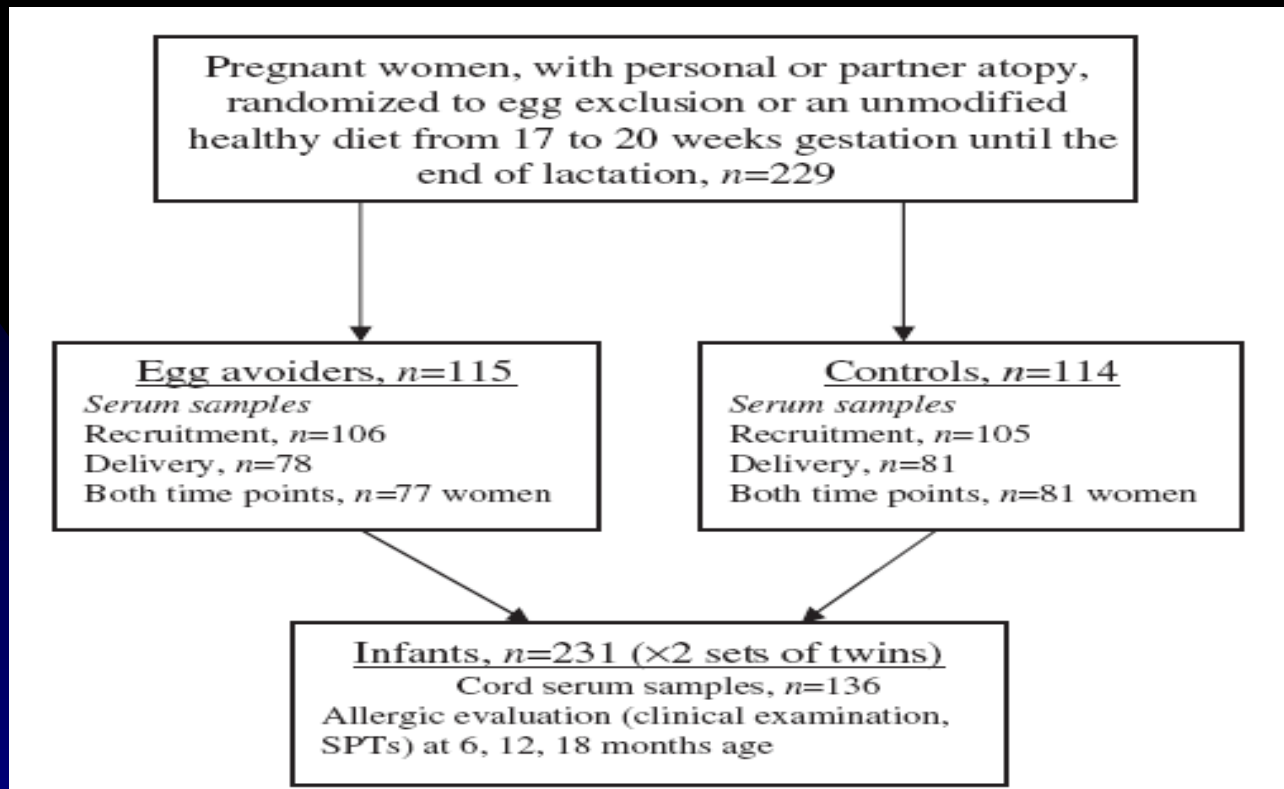
Conclusions. In the absence of anaphylaxis, the primary reliance on serum food-specific IgE testing to determine the need for a food elimination diet is not sufficient, especially in children with atopic dermatitis. In those circumstances, oral food challenges may be indicated to confirm food allergy status

Fleischer MD et al, J Pediatr 2011; 158: 678-83

Serum ovalbumin-specific immunoglobulin G responses during pregnancy reflect maternal intake of dietary egg and relate to the development of allergy in early infancy

Objectives: To monitor egg intake during a randomized controlled trial of egg avoidance throughout pregnancy and lactation by serial measurements of serum ovalbumin (OVA) IgG concentration in conjunction with dietary diary record and also, to analyse specific IgG concentrations at birth in relation to infant allergic outcome.

Methods: Pregnant women, with personal or partner atopy, were randomized to complete dietary egg exclusion or an unmodified healthy diet before 20 weeks gestation. The infants were examined carefully for signs of allergic disease and at 6, 12 and 18 months of age they were skin prick tested to a panel of common dietary and inhalant allergens (raw cow milk, whole egg, egg white, egg yolk, peanut, HDM, cat, timothy grass pollen, birch pollen: ALK).



Risultati: An atopic phenotype, as defined by atopic dermatitis and/or positive SPT, was identified in 47%, 55% and 42% of these infants at 6, 12 and 18 months of age, respectively. There was no difference in the number of infants born to egg-avoiding, as compared with control, mothers who developed an allergic phenotype over the first 18 months of life.

Highly accurate prediction of food challenge outcome using routinely available clinical data

TABLE IV. The estimators, relative risk and confidence intervals (Phase 2) presented separately for peanut, milk and egg ($P < .05$)

Allergen	Indicators	b-estimate	95% CI	Relative risk‡	95% CI
Peanut*					
	Male	4.60	± 3.4	8.6	4.5-16.4
Grade of symptoms†	1	3.32	± 3.2	4.4	2.8-7.1
	2	4.61	± 3.5	8.8	4.6-17.0
	3	7.86	± 4.6	12.8	6.0-26.2
	4	11.08	± 7.8	18.4	10.1-34.3
	SPT (mm)	2.85	± 1.3	3.8	2.7-5.4
	sIgE (kUa/L)	0.50	± 0.2	1.3	1.0-1.9
	IgE-sIgE (kUa)	-0.002	± 0.001	1.1	0.8-1.4
	Age (y)	-0.37	± 0.2	0.9	0.7-1.2
	Constant	-11.63	± 8.2		
Egg*					
	Male	1.70	± 1.5	2.2	1.5-3.1
Grade of symptoms†	1	1.40	± 1.2	1.9	1.3-2.8
	2	2.08	± 1.7	2.6	1.7-3.7
	3	2.74	± 2.1	3.5	2.2-5.4
	4	3.76	± 2.7	5.5	3.2-9.1
	SPT (mm)	0.29	± 0.1	1.2	0.5-3.7
	IgE-sIgE (kUa)	-0.004	± 0.001	1.1	0.7-2.1
	sIgE (kUa/L)	0.20	± 0.1	1.1	0.6-2.3
	Age (y)	-0.15	± 0.1	0.9	0.3-2.2
	Constant	-2.42	± 1.4		
Milk*					
	Male	0.59	± 0.3	1.4	1.1-1.6
Grade of symptoms†	1	0.48	± 0.2	1.3	0.8-2.3
	2	2.36	± 1.3	1.7	1.0-3.0
	3	7.92	± 4.1	4.4	2.1-9.0
	4	8.51	± 5.7	5.1	2.5-9.3
	SPT (mm)	0.35	± 0.22	1.2	0.7-2.1
	IgE-sIgE (kUa)	-0.006	± 0.002	1.1	0.7-2.0
	sIgE (kUa/L)	1.8	± 0.8	2.6	1.2-6.8
	Age (y)	-0.15	± 0.1	0.9	0.6-1.6
	Constant	-14.61	± 9.3		

Data from group B.

*Food being challenged.

†Each of the 4 levels is has its own estimator with no symptoms (0) as the indicator: 1, skin or oral or gastrointestinal or upper respiratory only; 2, upper respiratory and gastrointestinal or 2 systems; 3, lower respiratory or 3 systems; 4, cardiovascular or 4 systems.

‡Corresponds to a 1-unit increase.

La gravità della reazione clinica precedente è il fattore di rischio più importante per la positività del successivo TPO

DunnGalvin A et al, JACI 2011; 127: 633-39

Reazioni durante il TPO nella letteratura

Autore	TPO (n)	TPO pos (%)	Sintomi respiratori # (%)	Sintomi cardiovascolari (%)	Adrenalina (%)
Reibel, 2000	349	51	2.8	0	?
Perry, 2004	584	43	26	0	11
Mankad, 2008	150	27	8	0	0
Jarvinen, 2009	1273	34	0	0	11
Lieberman, 2011*	701	18.8	2.2	0	9
Calvani submitted	526	48.3	20.4	0	0.4

sintomi del laringe o delle basse vie

* popolazione a rischio relativamente basso di allergia

A new model for low-dose food challenge in children with allergy to milk or egg

Background: Atopic eczema and food allergy are common in early childhood. Children seem to gradually develop tolerance to milk and egg, and it is a relief for families when their child can tolerate small amounts of these basic foods, even if larger doses may still cause symptoms.

Aim: To develop a model for low-dose oral food challenge, facilitating re-introduction of milk or egg.

Methods: In 39 children sensitized to milk and/or egg, we performed 52 challenges using a new standardized model for low-dose oral food challenge

Increasing doses of the allergen were given in amounts of 0.1, 0.5, 5.0, 15 and 30 ml for milk and 0.1, 0.5, 1.5, 5 and 10 g (di un dolce preparato con uovo) for egg.

A new model for low-dose food challenge in children with allergy to milk or egg

Outcome of food challenge

In 4/52 challenges the results were positive, with immediate allergic symptoms. All four children had a family history of allergy. They were subjected to DBPCFC to milk and reacted on the first to third dose administered. One child had a negative SPT at the time of the challenge but expressed an SPT of 10.5 mm when re-tested 2 wk after the challenge.

Post food challenge follow-up

At the 3-mo follow-up, three of the four children with a positive challenge outcome were still on a milk and egg-free diet. At its parents' initiative, one child (child 1, Table III) had received small amounts of milk in its diet without problems. All but two of the non-reacting infants had successfully introduced the food into their diet without reactions.

Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children

TABLE II. Demographics of subjects of 436 positive OFCs that were treated or not treated with epinephrine

	Epinephrine N = 50	No epinephrine N = 386	P value
Age (y), median (25% to 75%)	7.9 (5-10.5)	5.8 (4-8.5)	<.001
Male sex, n (%)	30 (60)	223 (57)	.89
Asthma, n (%)	27 (54)	122 (31)	.369
History of anaphylaxis, n (%)	79 (20)	10 (20)	1.0
Specific IgE (kU _A /L), median (25% to 75%)	1.4 (0.47-6.4)	1.8 (0.58-4.6)	.79
SPT wheal (mm), median (25%-75%)	6 (4-7.3)	6 (4-7.1)	.55
Food†			
Cow's milk (n = 115), n (%)	14 (12)	101 (88)	.95†
Hen's egg (n = 74), n (%)	15 (16)	81 (84)	.13†
Peanut (n = 38), n (%)	10 (26)	28 (74)	.006†
Soy (n = 40), n (%)	3 (7)	37 (93)	.57†
Wheat (n = 34), n (%)	3 (9)	31 (91)	.82†
Fish (n = 11), n (%)	1 (9)	10 (91)	.82†
Tree nuts (n = 12), n (%)	4 (33)	8 (67)	.051†
Seed (sesame, mustard; n = 6), n (%)	0	6 (100)	.81†
Shellfish (n = 2), n (%)	0	2 (100)	.55†
Other food‡ (n = 82), n (%)	0	82 (100)	<.001*†
Type of OFC			
DBPCFC (n = 171), n (%)	16 (9)	155 (91)	.36§
SBPCFC (n = 80), n (%)	10 (12)	70 (88)	.95§
Open (n = 160), n (%)	12 (7)	148 (93)	.07§
Not defined (n = 15), n (%)	2 (13)	13 (87)	.80§
Median percentage of food (25% to 75%) eliciting reaction of the total challenge dose	35% (15-75)	40% (10-100)	.79

Le reazioni al challenge che richiedevano Adrenalina si verificano più spesso nei bambini di età più elevata e se allergici alle arachidi. Il Sesso, la storia di anafilassi o di asma o i valori delle IgE specifiche non erano fattore di rischio

Jarvinen KM et al, J Allergy Clin Immunol 2009; 124: 1267-72

Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy

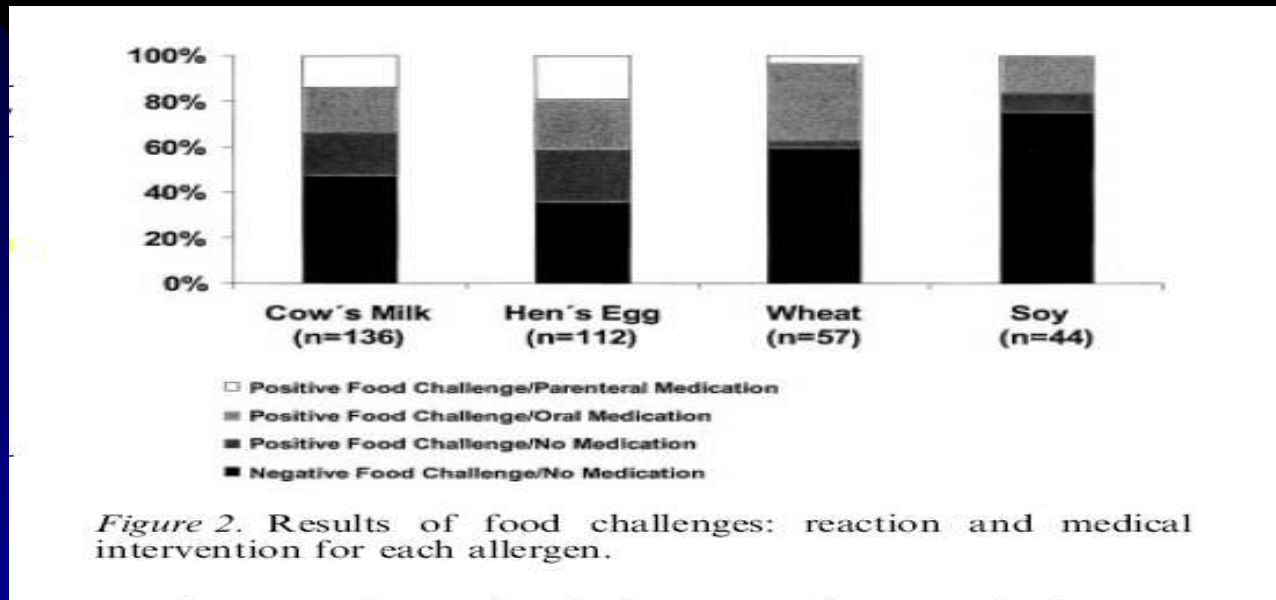
The goal of this study was to assess (i) parental anxiety about food-allergic reactions in their child and (ii) the association between a doubleblind placebo-controlled food challenge (DBPCFC) and parental anxiety about foodallergic reactions in their child.

Psychological measures

We used the Spielburger State-Trait Anxiety Inventory (STAI), Dutch Version (17), to assess two types of anxiety: state anxiety (transient emotional condition, in this study anxiety about a food-allergic reaction) and trait anxiety (disposition indicating anxiety proneness).

What safety measures need to be taken in oral food challenges in children?

Methods: We retrospectively evaluated 349 oral challenges in 204 children with atopic dermatitis, looking for criteria to help the physician decide which patients need medical intervention.



Of the 178 (51%) positive provocations, 120 (67%) subjects needed medical intervention, and 58 (33%) had a positive challenge but needed no medication. In 42 (23%) food challenges, medical intervention was parenteral, and oral medication was given in 78 (43%) cases (Fig. 1).

Risk of oral food challenges

Metodi: analisi retrospettiva delle cartelle dei bambini sottoposti a test di scatenamento orale per alimenti in un periodo di 7 anni

Popolazione: di 584 challenge, 253 (43%) hanno dato esito ad una reazione allergica. In particolare per quanto riguarda il latte, 90/161 (56%) sono falliti (reazione allergica)

Briefly, challenges were administered in escalating doses every 15 minutes until 4 g (<5 years old) or 8 g (5 years old) of food protein was ingested. The challenge was terminated when objective symptoms were noted by the practitioner or subjective symptoms such as abdominal pain worsened during the challenge.

Risk of oral food challenges

TABLE III. Severity of reactions during failed food challenges

	Milk N = 90	Egg N = 56	Peanut N = 71	Soy N = 21	Wheat N = 15	Total N = 253
Mild	33 (37%)	18 (32%)	28 (39%)	9 (43%)	10 (67%)	98 (39%)
Moderate	33 (37%)	17 (30%)	25 (35%)	8 (38%)	0 (0%)	83 (33%)
Severe	24 (27%)	21 (38%)	18 (25%)	4 (19%)	5 (33%)	72 (28%)

That severe allergic reactions occur during OFC is not in doubt, and the procedure must take place in appropriately staffed children's units with adequate resuscitation facilities. Such reactions appear to be treated effectively without harmful effects to the patient, with no cases of very severe or fatal allergic reactions identified in a two year period

Is this apparently reassuring finding a reflection of our reluctance to investigate children when the tests may put them at risk?

Safety of open food challenges in the office setting

Table 2. Organ System Involvement and Reaction Severity for Positive Challenges^a

Variable	Milk (n = 4)	Peanut (n = 12)	Egg (n = 13)	Other (n = 11)	Total (N = 40) ^b
Organ system ^c					
Skin	3	8	12	4	27 (68)
Upper respiratory tract ^d	0	6	3	6	15 (38)
Lower respiratory tract	0	0	1	2	3 (8)
Gastrointestinal tract	2	2	8	6	18 (45)
>1 Organ system	1	4	9	5	19 (48)
Reaction severity					
Mild	2	10	4	3	19 (48)
Moderate	2	2	8	6	18 (45)
Severe	0	0	1	2	3 (8)

^a Data are given as number of patients unless otherwise indicated.

^b Data are given as number (percentage) of the total.

^c There were no positive challenges with cardiovascular system involvement.

^d Excludes any laryngeal symptoms.

Challenges were judged positive and terminated **at the first sign of a convincing clinical reaction, resulting in objective findings based on the judgment of the practitioner administering the challenge.** **Conclusion:** Open food challenges are a safe procedure in the office setting for patients selected based on history and food specific IgE approaching negative predictive values

Outcomes of office-based, open food challenges in the management of food allergy

. The OFCs were performed **in the outpatient setting** by a trained nurse or physician (while the supervising physician was on site at all times) per guidelines established by the current Working Group on Food Challenges report, with most challenges using doubling doses every 15 minutes until an age-appropriate serving size was administered. **The majority of reactions, 56.8%, were cutaneous.** All but 16 reactions (87.9%) were treated with antihistamine alone. Twelve reactions were treated with epinephrine (including one that required 2 doses of epinephrine), 7 with prednisolone, and 2 with albuterol (Table III). **All but one reaction was managed in the office setting; 1 patient was transferred to the emergency department for monitoring and intravenous fluids due to persistent vomiting following a challenge to peanut.**

- Urisu A, Ando H, Morita Y, et al. Allergenic activity of heated and ovomucoiddepleted
- egg white. J Allergy Clin Immunol 1997; 100:171–176.

Risk factors for severe pediatric food anaphylaxis in Italy

Table 2 Food trigger of anaphylaxis and mean age of children studied

Food	Anaphylaxis					Age (yr)	
	N Children	Mild (%)	Moderate (%)	Severe (%)	All (%)	Median	Interquartile range
Cow's milk	47	21	60	19	29	3	1-5
Egg	25	28	32	40	15	1	0.5-4.5
Other	19	26	63	10	12	7	2-11
Unknown food*	15	20	53	27	9	8	3-12
Hazelnut	9	22	78	0	5	6	2-11
Kiwi	7	29	71	0	4	4	4-14
Peanut	6	17	33	50	4	3.5	1.8-5.8
Walnut	6	33	50	17	4	3	1.8-5.5
Pine nut	5	20	60	20	3	9	4-10.5
Unknown fish*	5	0	20	80	3	5	2-6
Wheat	4	0	100	0	2	0.5	0-10.8
Shrimp	3	33	67	0	2	11	10-13
Gad	3	33	33	33	2	8	2-9
Apricot	3	67	33	0	2	3	2-11
Sesame	3	0	67	33	2	4	3-10
Soy	3	0	100	0	2	2	1-3

*Children who developed anaphylaxis after a meal containing various types of food (or fish) and who were sensitized to more than one of them.

Cotto o crudo

- Ben cotto (180° x 20 min)(sponge cake baked) (Clark 2011)
- Cotto (bollito 60' a 90° (Ando 2008)
- Cotto (bollito 10' a 100° (Alessandri 2011)

Molecular diagnosis of egg allergy

Table 1 Major egg white allergens^a

Allergen	Common name	Constitute (%)	Mw (kDa)	Carbohydrate (%)	IgE binding activity			Test code ^b (in-vitro tests)
					Heat-treated	Digestive enzyme-treated	Allergenic activity	
Gal d 1	Ovomucoid	11	28	25	Stable	Stable	+++	f233
Gal d 2	Ovalbumin	54	45	3	Unstable	Unstable	++	f232
Gal d 3	Ovotransferrin/conalbumin	12	76.6	2.6	Unstable	Unstable	+	f323
Gal d 4	Lysozyme	3.4	14.3	0	Unstable	Unstable	++	k208

^a Reproduced with authorization from Benhamou AH, state of the art for egg allergy, *Allergy* 2010, 65:283–289.

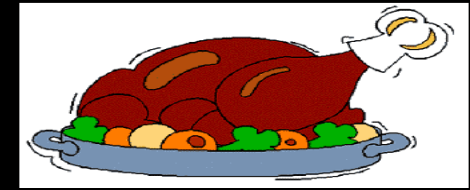
^b Test code for in-vitro UniCAP system.

Conclusion

Molecular diagnosis technologies will improve diagnosis of IgE-mediated egg allergy. .. Component-resolved diagnosis based on a microarray platform is especially promising. None of these molecular-based tests is ready to be used in clinical practice and an oral food challenge will still be necessary in many patients for the diagnosis of egg allergy.

Cauet JC et al, *Curr Opin Allergy Clin Immunol* 2011; 11: 210-5

Nicola, 14 anni



Affetto da rinite primaverile da graminacee, polisensibilizzato a pollini ed epiteli di animali, in trattamento da 2 anni, con giovamento, con vaccino desensibilizzante per graminacee.

Riferisce che da circa 4 anni ha iniziato a presentare dei sintomi, progressivamente ingravescenti di prurito orale, “saliva densa”, fastidio alla gola che si protraggono per circa ½ ora, che insorgono subito dopo aver assunto il pollo. Per tale motivo da circa 2 anni ha smesso di assumerlo. Tali sintomi si sono presentati in modo importante inoltre in seguito alla assunzione di una fettina di tacchino, che quindi non ha più assunto. Si presentano invece in forma lieve quando mangia dei wurstel di maiale, non se i wurstel vengono cotti bene, e per questo motivo ancora li assume.

Assume invece abitualmente e senza alcun disturbo l'uovo, in tutte le forme. Da 2 anni inoltre ha iniziato a presentare una analoga sintomatologia, in più occasioni, subito dopo aver mangiato del tonno e anche del merluzzo, che quindi ha smesso di mangiare, mentre assume senza problemi altri pesci, quali spigola, orata e anche i crostacei e i molluschi.



Gli accertamenti eseguiti

CAP

Pollo: 1.6 ku/l
Tacchino: 0.78
Albume: neg
Tuorlo: neg

SPT

Albume: 1 mm
Tuorlo: 2 mm
Pollo: 6 mm
Maiale: 3 mm
Merluzzo: 5 mm
Tonno: 4 mm
Sardina: 4 mm
Gambero: neg
Mitili: neg
Istamina: 6 mm
Controllo: neg



UOVO DI GALLINA

Soluzione acquosa di oltre 40 proteine, **almeno 24 frazioni antigeniche diverse**

ALLERGENE	NOME	PM (kd)	AA	PREVALENTI NEL
Ovomucoide	Gal d1	28	186	albume
Ovoalbumina	Gal d2	66-70	385	albume
Ovotrasferrina	Gal d3	77	686	albume
Lisozima	Gal d4	14.3	129	albume
Ovomucina	Gal d ovomucina			albume
Alfa livetina	Gal d5			albume/tuorlo/carne/epiteli
Immunoglobuline	Gal dIgY			albume
Apovitellenina 1	Gal apovitellina I			tuorlo
Apovitellenina VI	Gal d apovitellina VI			tuorlo
Fosvitina	Gal d fosvitina			tuorlo
Etc..				

Peculiarities of egg allergy in children with bird protein sensitization

Disegno: gli autori hanno seguito prospetticamente per 4 anni 27 bambini con allergia all'uovo e alle piume di uccello o alla carne di pollo e 19 controlli con sola allergia all'uovo, per valutare se vi erano differenze nella evoluzione clinica.

Risultati: i bambini con allergia all'uovo e alle piume hanno una prognosi peggiore, per la maggior durata della allergia, la più frequente presenza di sintomi respiratori e gastrointestinali. Si differenziano dai controlli anche per il persistere e l'aumentare delle IgE specifiche per il tuorlo dell'uovo

Table 3. Diagnostic Data of Patients with Egg Allergy

	Sensitized to birds n = 27	Controls n = 19
At the start of the study		
Positive prick to egg white	27	19
Positive prick to egg yolk	26	19
Mean IgE to egg white (KU/l)	23.6	9.6
Mean IgE to egg yolk (KU/L)	12.5*	0.8
Egg-challenge†	8/8	5/5
Chicken meat challenge†	2/2	0/0
At 4 years follow-up		
Patients with persisting egg allergy	23	8
Positive prick to egg white	23	8
Positive prick to egg yolk	23	7
Mean IgE to egg white (KU/L)	38.9*	12.7
Mean IgE to egg yolk (KU/L)	51.4*	2.7
Egg challenged†	9/5	13/2
Chicken meat challenge†	4/0	0/0

* $P < .001$ and † done/positive.

La Egg-bird o la Bird-egg Syndrome è dovuta alla alfa-livetina (Gal d5)

Food allergy to chicken meat with IgE reactivity to muscle α -parvalbumin

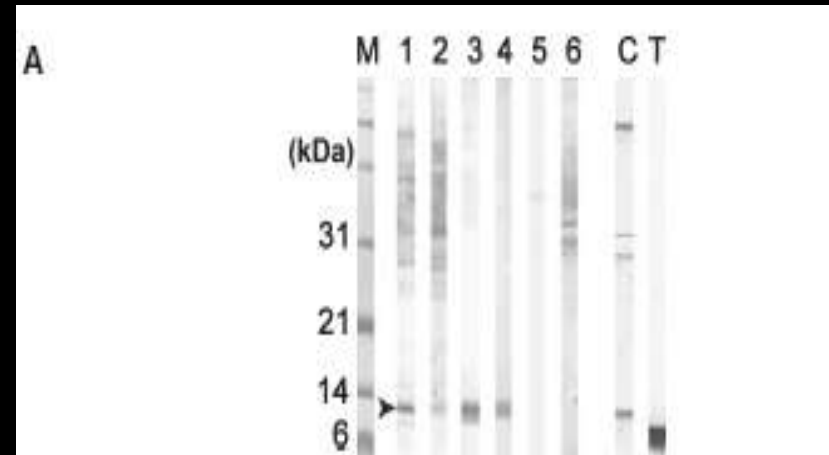
We report the case of a 54-year-old patient who experienced severe allergic reactions to poultry products. Swelling of tongue and oral mucosa, vomiting and hypotension occurred a few minutes after ingestion of chicken meat, turkey meat or chicken both. The patient reported mild oral reactions when eating tuna and salmon. The patient tolerated chicken eggs.

Skin prick tests (SPT) performed with a series of commercial aeroallergens (ALK, Varennes en Argonne, France) were positive for tree and grass pollen. Skin prick tests with food allergens were positive with chicken meat, turkey meat and different fishes (tuna, salmon, cod and carp).

Food allergy to chicken meat with IgE reactivity to muscle α -parvalbumin

The total IgE level was 80 kU/l (Phadia ImmunoCAP System, Uppsala, Sweden). Specific IgE were positive for chicken meat (12 kU/l), turkey meat (6 kU/l), pork meat (1 kU/l), cod (3 kU/l), tuna (3 kU/l) and salmon (2 kU/l), but negative for egg yolk and egg white (<0.35 kU/l).

Protein sequence analysis of α -parvalbumins showed that chicken parvalbumin was 100% identical to turkey, 83% to cattle/horse, 82% to frog, 80% to pig, 79% to human (X63070) and 54% to cod β -parvalbumin. IgE bind specifically to purified native (3) and recombinant (4) chicken α -parvalbumin, but not to tuna (5) β -parvalbumin



Identification of Allergens in Chicken Meat Allergy

A 20-year-old man experienced oropharyngeal and palmar itching, facial hives, lip swelling, dysphagia, dyspnea, and heartburn 15 minutes after eating chicken. He tolerated turkey, but did not eat any other poultry meat or meats such as veal, pork, and rabbit. He tolerated eggs and had no contact with birds

The analysis of the resulting peptides by mass spectrometry or MS/MS identified the 16-kDa band as α -parvalbumin and the 27-kDa band as myosin light chain 1 (MLC). We present a patient with IgE-mediated allergy to chicken meat and no sensitization to egg proteins. α -Parvalbumin and myosin were identified as the relevant allergens

Table. Results of Skin Test and Specific Immunoglobulin E Determinations

	Skin Tests			Specific IgE	
	Commercial SPT	Prick-by-Prick	Extract SPT, 10 mg/mL	Phadia CAP system, KU _A /L	EAST technique, KU _A /L
Chicken	0	NP	NP	<0.35	NP
Veal	0	NP	NP	<0.35	NP
Pork	0	NP	NP	<0.35	NP
Lamb	0	NP	NP	<0.35	NP
Chicken, raw	NP	4	4	NP	<0.35
Chicken, boiled	NP	3	5	NP	0.6
Turkey, raw	NP	4	5	NP	<0.35
Turkey, boiled	NP	7	11	NP	0.6
Duck, raw	NP	5	7	NP	<0.35
Duck, boiled	NP	5	5	NP	0.4
Quail, raw	NP	0	8	NP	<0.35
Quail, boiled	NP	3	9	NP	0.6
Ostrich, raw	NP	NP	4	NP	<0.35
Ostrich, boiled	NP	NP	4	NP	0.4
White	0	NP	0	<0.35	<0.35
Yolk	0	NP	0	<0.35	<0.35
Ovoalbumin	0	NP	NP	<0.35	NP
Ovomucoid	0	NP	NP	<0.35	NP
Chicken feathers	0	NP	NP	<0.35	<0.35
Histamine	6				
Saline solution	0				
Total IgE	36.2 IU/mL				

Abbreviations: Ig, immunoglobulin; NP, not performed; SPT, skin prick test.

Identification of Allergens in Chicken Meat Allergy

α -Parvalbumin is abundant in the muscle of fish and amphibians, rather less so in birds and mammals, and is not generally described as allergenic, except for a case of allergy to frog meat [6] and a case of allergy to poultry meat [4]. β -Parvalbumin, which does not usually cross-react with α -parvalbumin [7], has been described as a major allergen and as the most important allergen in many fish species. Myosins are a large superfamily of motor proteins that move along actin filaments while hydrolyzing adenosine triphosphate.

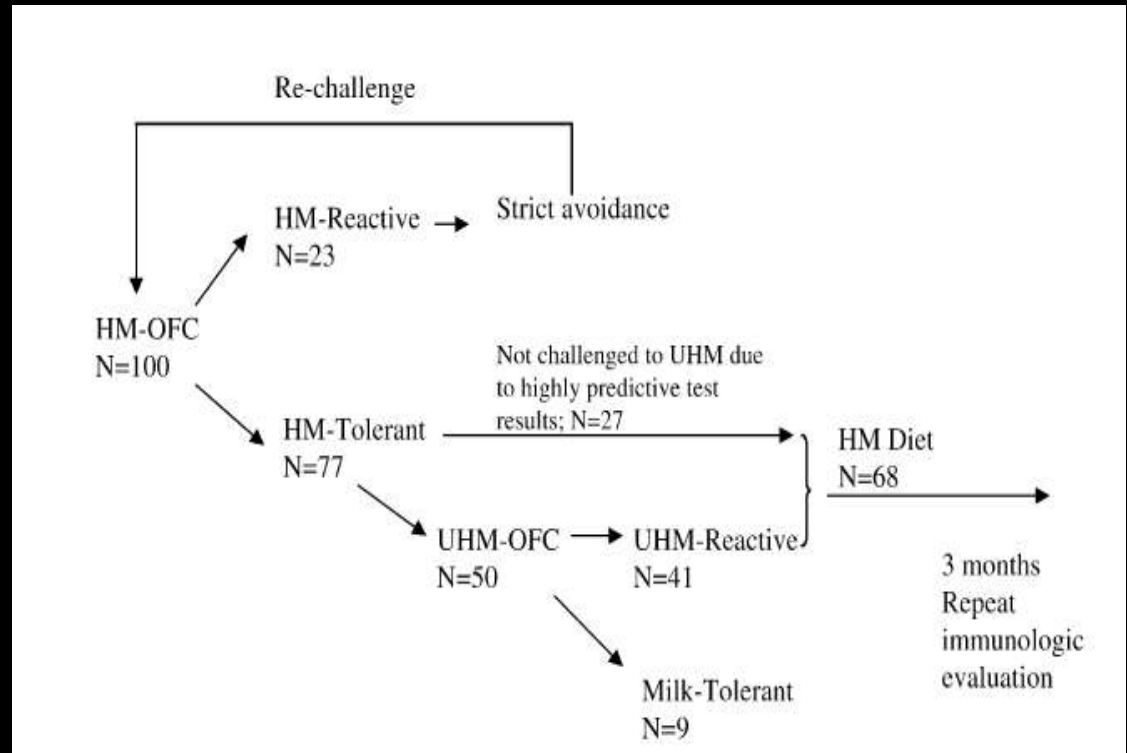
Two light chains of muscle myosin, each measuring 20 kDa, wrap around the neck region of the 2 myosin heavy chains [8]. Although shrimp MLC (Lit v 3) has been identified as a new major shrimp allergen [8], MLC has never been described as an allergen in chicken meat.

Tolerance to extensively heated milk in children with cow's milk allergy

100 bambini di 6 mesi-21 anni (media 7.5 anni) con SPT o IgE specifiche per latte e storia di reazione entro 6 mesi o valori superiori ai cut-off consigliati

68/100 bambini tolleravano il latte cotto in matrice di grano

Ciascun muffin e waffle contenevano 1.3 gr di proteine del latte. Il TPO consisteva nella somministrazione di 1 muffin e 1 waffle (2.6 gr)



Muffin cotto a 350°F (176° celsius) per 30 minuti
Waffle cotto a 500° F (260° celsius) per 3 minuti

Tolerance to extensively heated milk in children with cow's milk allergy

Tutti i bambini con negatività delle IgE specifiche o SPT < 5 mm per il latte tolleravano il latte cotto

8/23 dei bambini che hanno reagito al latte cotto hanno sviluppato anafilassi contro 0/41 di quelli che reagivano al latte non cotto

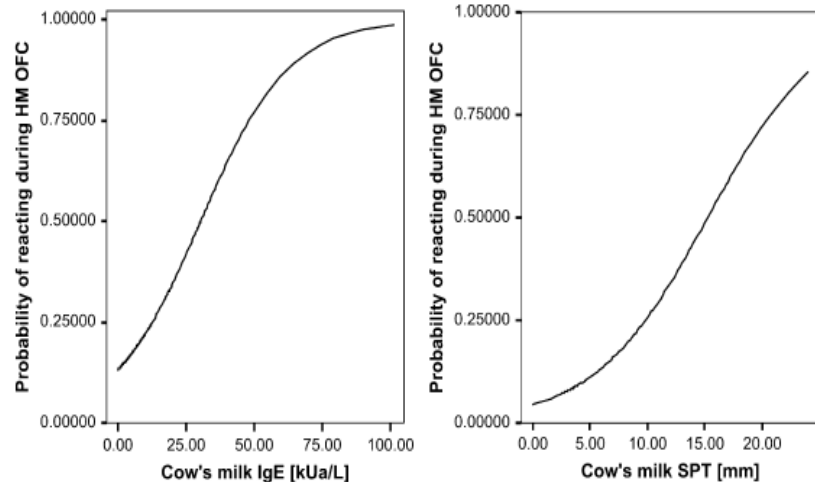


FIG 2. Predicted probabilities of the heated milk challenge outcome in regard to milk-specific IgE and SPT. Logistic regression was used to calculate the probability of reacting during heated milk (HM) oral food challenge (OFC) in regard to serum milk-specific IgE antibody concentration and SPT wheal size.

TABLE III. Percent tolerating heated milk oral food challenge in comparison with milk-specific IgE and SPT

Milk IgE (kU _A /L)	<0.35	0.35 to <5	5 to <20	20-100	<35	>15	>35
Tolerant	6/6 (100%)	51/57 (89.5%)	12/18 (66.7%)	4/14 (28.6%)	72/89 (80.9%)	6/17 (35.3%)	1/7 (14.3%)
Milk SPT wheal (mm)	0 to <3	3 to <5	5 to <8	<10	≥8	≥10	>14
Tolerant	2/2 (100%)	7/7 (100%)	32/39 (82.1%)	58/68 (85.3%)	31/45 (68.9%)	15/25 (60%)	2/6 (33.3)

Milk-specific IgE ≥15 kU_A/L and milk SPT wheal ≥8 mm have a 95% predictive value for acute reactions during an oral challenge with nonheated milk.^{15,16}

Tolerance to extensively heated milk in children with cow's milk allergy

Dopo 3 mesi di continua assunzione degli alimenti contenenti latte cotto si assisteva ad una significativa riduzione del diametro del pomfo per il latte e ad un aumento delle IgG₄ per la caseina

TABLE II. Comparison of baseline and 3-month immunologic parameters in heated milk-tolerant subjects

	Baseline median (range)	3-Month median (range)	<i>P</i> value*
Milk SPT, wheal size (mm)	8 (2.5-19)	7 (2-10.5)	.001
Milk IgE (kU _A /L)	2.5 (0-79.1)	1.99 (0-76)	.493
Casein IgE (mg _A /L)	1.29 (0-101)	1.6 (0-84)	.769
β-Lactoglobulin IgE (mg _A /L)	0.15 (0-63.7)	0.49 (0-18.7)	.758
Casein IgG ₄ (mg _A /L)	0.54 (0-8.1)	1.02 (0.05-14.7)	.005
β-Lactoglobulin IgG ₄ (mg _A /L)	0.29 (0-11.3)	0.49 (0-31)	.328
Undetectable casein IgG ₄ (%)	6 (12)	0 (0)	.027 †
Undetectable β-lactoglobulin IgG ₄ (%)	7 (14.3)	6 (12)	1.0‡
Casein IgE/IgG ₄ ratio	1.43 (0-131.2)	1.38 (0-55.4)	.148
β-Lactoglobulin IgE/IgG ₄ ratio	0.23 (0-235.9)	0.49 (0-17.4)	.319

Statistically significant *P* values are in boldface text.

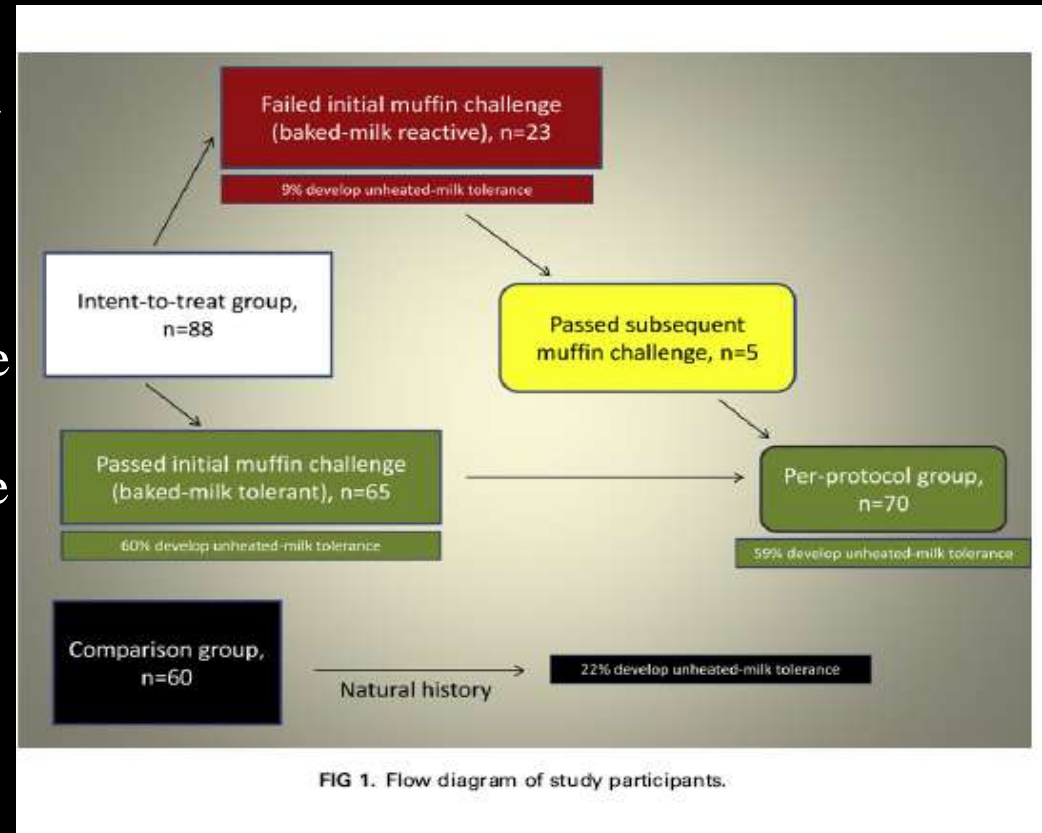
Determined by using *the paired *t* test or Wilcoxon signed-rank test, †Fisher exact test, and ‡χ² test. *P* value less than .05 was considered statistically significant.

.. our findings suggest that ingestion of heated milk is associated with responses to casein and b-lactoglobulin that favor development of tolerance.

Nowak Wegrzyn A et al, J Allergy Clin Immunol 2008

Dietary baked milk accelerates the resolution of cow's milk allergy in children

- Dei 65 bambini che hanno tollerato il latte cotto,
- 39 (60%) tolleravano anche il latte non cotto **dopo 5 anni di follow-up**
 - 8 (12%) decidevano di tornare a dieta senza latte
 - 5 riferivano sintomi alla ingestione di prodotti meno cotti
 - 2 hanno avuto sintomi al challenge con latte non cotto
 - 1 ha avuto una reazione alla ingestione di un uovo con mozzarella
 - 2 hanno avuto sintomi orali alla ingestione di pizza poco cotta



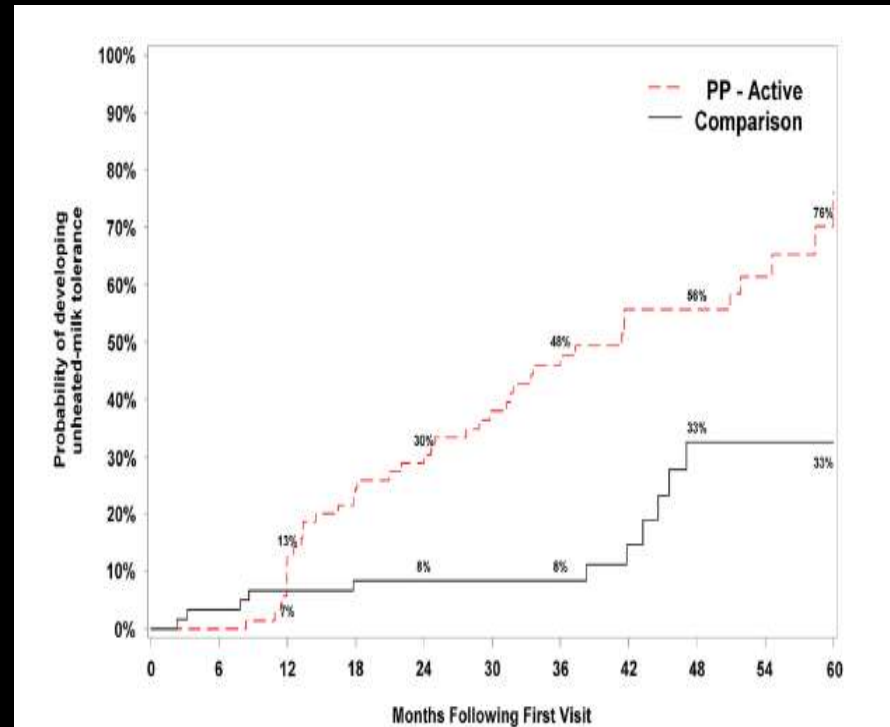
Dietary baked milk accelerates the resolution of cow's milk allergy in children

TABLE II. ORs for tolerance comparing the baked milk-tolerant versus baked milk-reactive groups

Final follow-up status	OR (95% CI)	P value
Unheated milk tolerant vs strict avoidance	27.8 (4.8-162.7)	<.001
Baked milk/cheese tolerant versus strict avoidance	8.7 (1.8-43.5)	.008

OR, Odds ratio.

In the per-protocol group (n = 70) the probability of having unheated milk tolerance within 60 months was 76%. In the comparison group (n = 60) this probability was 33%



Tolerance of baked milk is a marker of transient IgE-mediated cow's milk allergy, whereas reactivity to baked milk portends a more persistent phenotype. The addition of baked milk to the diet of children tolerating such foods appears to accelerate the development of unheated milk tolerance compared with strict avoidance

Differenze immunologiche nei soggetti con allergia al latte cotto in matrice o crudo

Jarvinen KM, JACI 2001

Five **IgE-binding epitopes** were not recognized by any of the patients with transient milk allergy but showed binding by the majority of the patients with persistent allergy.

Schreffler WG, JACI 2009

A higher percentage, 16.85% (7.1–31.7)] of **proliferating allergen-specific CD25+CD27+ T cells** from cultures of heated milk-tolerant children [4.91% (2.6–7.5)] than those with allergy.

Wanich N, JACI 2009

Heated milk-tolerant individuals' **basophils were significantly less responsive** to milk allergen stimulation at all doses than were basophils from heated milk-reactive individuals

Wang J, JACI 2010

Children with milk allergy **had increased epitope diversity** compared with those who outgrew milk allergy.

Caubet , submitted

levels of IgE to cow's milk, casein and b-lactoglobulin were significantly higher in baked milk-reactive patients compared with baked milk-tolerant patients

Immunologic changes in children with egg allergy ingesting extensively heated egg

Inizialmente arruolati 127 bambini (età media 6.9 anni). Dopo il TPO 27 erano allergici all'uovo cotto, 64 tolleravano l'uovo cotto in matrice di grano e 23 non allergici all'uovo. Quindi 70% (64/91) dei bambini con allergia all'uovo tolleravano l'uovo cotto

During each oral food challenge, a muffin and a waffle that each contained one third of an egg (approximately 2.2 g of egg protein) were ingested. The muffin was baked at 350F for 30 minutes in an oven, and the waffle (<0.625 inches thick to ensure thorough heating) was cooked in a waffle maker at approximately 500F for 3 minutes.

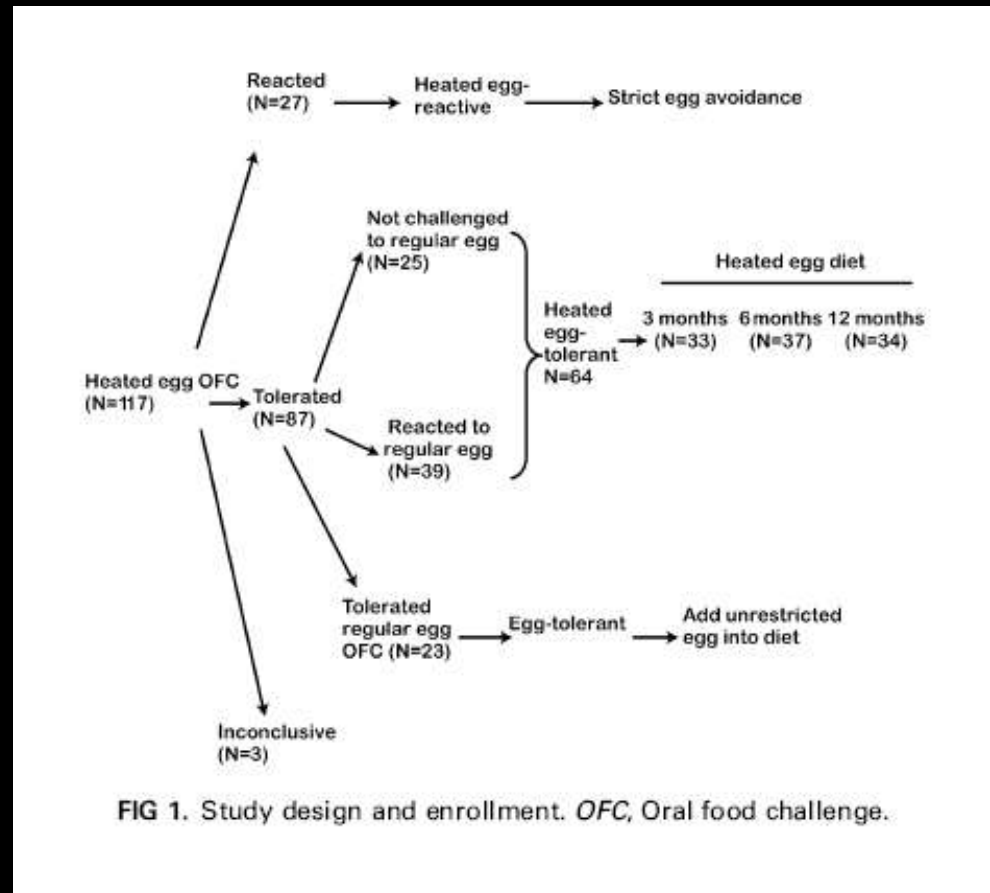


FIG 1. Study design and enrollment. OFC, Oral food challenge.

Immunologic changes in children with egg allergy ingesting extensively heated egg

Non vi era differenza nell'impiego di adrenalina negli allergici all'uovo crudo o cotto.

Coloro che ricevevano adrenalina avevano IgE specifiche per l'uovo (2.5 vs 0.7) e per l'ovomucoide (1.8 vs 0.5) più elevate degli altri e un rapporto IgE/IgG4 per ovomucoide più elevato.

Non c'era invece correlazione con la gravità della reazione

Le differenze comunque non erano tali da raggiungere un valore predittivo in grado di evitare il TPO

TABLE I. Challenge data clinical reactions

Parameter*	Extensively heated egg OFC (n = 27)	Scrambled egg/French toast (n = 39)
Symptoms		
Cutaneous	11	24
UA	19	27
LA	4	4
GI	11	18
CV	0	0
Treatment		
Epinephrine + other medications	5	9
Diphenhydramine only	14	23
Diphenhydramine + other medications (except epinephrine)	4	4
No treatment†	4	3
Eliciting dose (g) of egg protein, median (range)	2.0 (0.1-2.1)	1.5 (0.01-6)

OFC, Oral food challenge; Cutaneous, atopic dermatitis, urticaria, angioedema, rash, and pruritus; UA, upper airway (rhinorrhea, nasal congestion, sneezing, and oral pruritus); LA, lower airway (wheezing); GI, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain); CV, hypotension.

Numbers in each column represent the number of patients with specific symptoms on oral food challenge. Numbers in parentheses represent ranges.

*No statistical differences were observed between groups for any parameter.

†Subjects not treated with medications had transient allergic symptoms, including abdominal pain, a single episode of emesis, scattered urticaria, and oral pruritus.

25 bambini non hanno fatto il TPO con uovo crudo perché avevano le IgE specifiche > ai valori predittivi

Immunologic changes in children with egg allergy ingesting extensively heated egg

TABLE III. Follow-up immunologic parameters in children ingesting extensively heated egg

	Baseline	3 mo	P value	6 mo*	12 mo*
SPT (mm)	6 (5-8)	5 (3.4-7)	<.001	5 (3-7)	5 (3.5-6)
EW-specific IgE (kUA/L)	1.3 (0.6-4.3)	1.7 (0.6-5.2)	NS	1.7 (0.7-4.7)	1.3 (0.3-3.2)
OVA-specific IgE (kUA/L)	1.6 (0.7-4.7)	1.4 (0.5-4.9)	NS	1.6 (0.6-4.5)	1.1 (0.5-3.2)
OVM-specific IgE (kUA/L)	1.0 (0-3)	0.8 (0-3.3)	NS	1.2 (0.3-2.8)	1.0 (0.3-2.3)
OVA-specific IgG4 (μg/L)	0.4 (0-2)	4.6 (0.6-12.5)	<.001	3.1 (0.5-7.6)	3.1 (0.9-10)
OVM-specific IgG4 (μg/L)	0.1 (0-0.4)	0.6 (0.1-1.4)	<.001	0.5 (0.1-1.5)	0.6 (0.1-1.7)
OVA-specific IgE/IgG4 ratio	5.7 (1.7-81)	0.6 (0.1-2.9)	<.001	0.7 (0.1-2.9)	0.4 (0.03-0.5)
OVM-specific IgE/IgG4 ratio	7.4 (2-14.5)	1.1 (0.07- 3.3)	<.001	1.4 (0-6.7)	0.9 (0.2-4.2)

EW, Egg white; NS, not statistically significant ($P > .05$); OVA, ovalbumin; OVM, ovomucoid.

All numbers represent median values with 25% to 75% interquartile ranges provided in parentheses.

*No significant changes were noted in any of the parameters between the 3-, 6-, and 12-month follow-up intervals.

Nei bambini a dieta con uovo cotto in matrice di grano si assisteva ad una riduzione di alcuni parametri immunologici di sensibilizzazione allergica nei primi 3 mesi

Follow-up of the Heated Egg Clinical Trial

METHODS: HE-tolerant subjects incorporated HE into their diet and were periodically (every >6 months) challenged to less-heated-egg (LHE) in the form of egg noodles and meatballs, followed by RE. HE-reactive subjects were re-challenged to HE

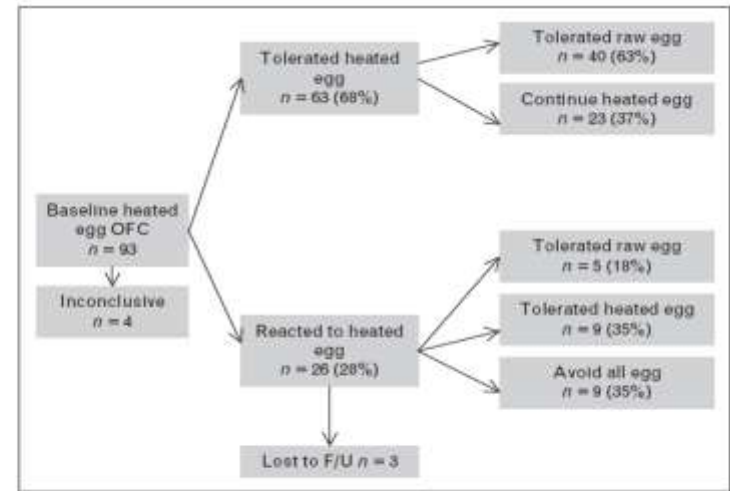


FIGURE 2. Study design and enrollment for baked egg trial. Adapted with permission from [29].

Patients who were initially baked egg tolerant were 3.3 times more likely to develop regular egg tolerance than those who were initially baked egg reactive. Patients in the active per-protocol group were 14.6 times more likely to develop regular egg tolerance than those in a retrospectively assessed comparison group who continued strict avoidance of egg and more likely to develop the tolerance earlier (median 22.0 versus 66.7 months; $P < 0.0001$). These findings suggest that the baked egg diet accelerates the development of regular egg tolerance when compared with strict avoidance.

Nowak-Wegrzyn A, J Allergy Clin Immunol 2011; 127:(Abstract)

L'Effetto Matrice

La cottura dell'uovo a 180° c per 10 minuti insieme al grano riduce la solubilità dell'ovomucoide. Lo stesso non avviene per la caseina. L'immunoblotting suggerisce che l'ovomucoide formi dei polimeri e dei complessi ad alto peso molecolare aggregandosi con il glutine, cosa che rende meno solubile l'ovomucoide. Questo spiega perché sia necessario un cut off più elevato per le IgE specifiche per l'ovomucoide per predire la reattività all'uovo cotto in matrice di grano.

Kato Y, Watanabe H, Matsuda T. Ovomucoid rendered insoluble by heating with wheat gluten but not with milk casein. *Biosci Biotechnol Biochem* 2000;64: 198-201

Extensively heated milk and egg as oral immunotherapy

Thermal processing can destroy IgE-binding conformational epitopes but usually does not destroy sequential IgE-binding epitopes, and this appears to play a role in milk and egg allergy. Food behavior under different heating conditions, as well as interactions with food matrix (e.g. as seen in the case of hen's egg white), are highly variable among different foods, and therefore, heating may not have similar effects for all foods. In addition, thermal processing may not simply alter IgE epitopes, as it can alter different biophysical and immunological properties of a food protein such as its structure, function, solubility, digestibility, and T-cell responses [22]. Some food proteins are rendered more allergenic by thermal processing. For peanut proteins, high temperature may enhance allergenicity as a result of glycation (Maillard reaction) that induces the formation of Ara h 2 aggregates that are more resistant to gastric digestion and bind IgE antibody more effectively than unheated Ara h 2

ICON: Food allergy

TREATMENT OPTIONS AND PREVENTION

The primary therapy for food allergy is strict avoidance of the causal food or foods. .. Although allergen avoidance is unproved in randomized controlled trials, it is the safest strategy for managing food allergy.

Treatment

Strict avoidance of allergens is not curative and leaves patients at risk for accidental exposure. **As such, several new therapeutic approaches are being tested in clinical trials, but none is ready for clinical care...** For a variety of food allergens, **oral immunotherapy is effective in reducing clinical reactivity in some patients, but its ability to induce tolerance remains uncertain.** **In addition, the approach places patients at risk for severe reactions and is therefore not appropriate for widespread use.** **Diets containing extensively heated (baked) milk and egg might represent an alternative approach to food oral immunotherapy; however, further studies of this approach are necessary**

Burks WA et al, JACI 2012, in press

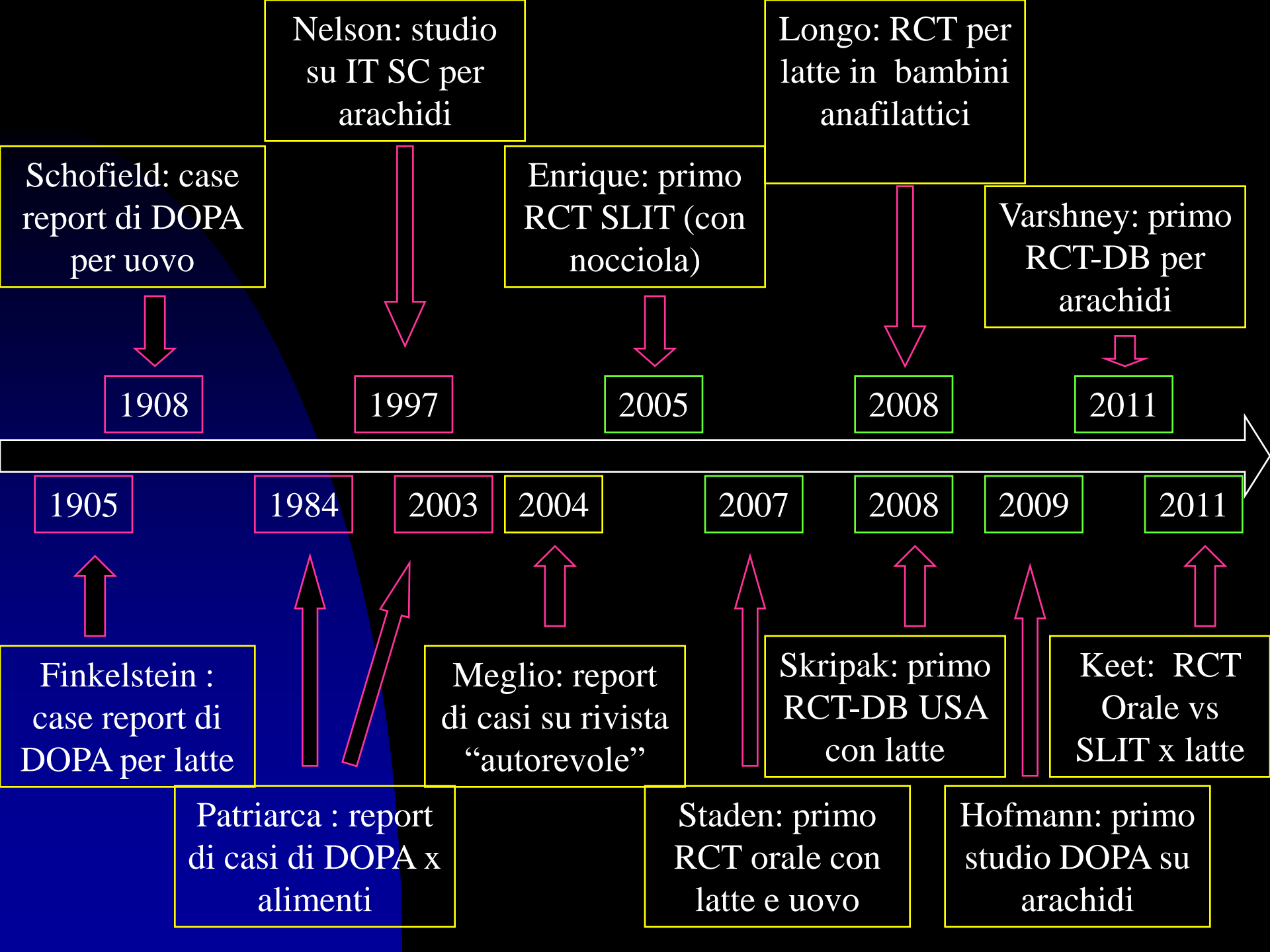
Treatment Rather Than Avoidance May Be Within Reach for Children With Food Allergies

“All the investigators who conduct controlled trials are concerned because we see a lot of adverse reactions” with the therapy, said Sampson. “If a bad accident happened because of oral immunotherapy, it could make it pretty difficult for us to continue research”

An expanding evidence base provides food for thought to avoid indigestion in managing difficult dilemmas in food allergy

Although there is a notion that strict avoidance speeds recovery and delayed introduction of foods prevents allergy, various studies are modifying our understanding of this dogma and changing how we might present dietary information to parents. For example, recurrence of peanut allergy has been noted when tolerated ingestion was not continued.....

Infants are not mice, but assessment of the risks and benefits of diet avoidance are becoming more complex and less certain. Perhaps tolerated exposure speeds, rather than hinders, recovery from an allergy for some children.



- 1) cosa ha contribuito a insinuare la possibilità di desensibilizzare gli allergici alimentari? Una serie di dati, tra cui studi preliminari che ne dimostravano l'efficacia
- 2) a chi va indirizzata la desensibilizzazione per alimenti? ai tolleranti parziali o ai superallergici?

	Autore	Tipo	Tipo di studio	Tipo protocollo	Alimento	Reazioni avverse	Insuccessi
1	Patriarca G, Allergol Immunopathol 1984	Orale	Aperto	Lento	Lalle/uoovo/pesce	-	6,7
2	Wutrich, Monogr All 1996	Orale	Aperto	Lento	Latte	?	25
3	Patriarca G, Hepatogastroenterol 1998	Orale	Aperto	Lento	Latteluovo/pesce/mela	71,4	15,3
4	Patriarca, AI PharmTher 2003	Orale	Aperto con controllo	Lento	Latte/uoovo/pesce	67,8	16,7
5	Bauer, Abstract 2004	Orale	Aperto	Rush	Latte	100	11,1
6	Longo, Med e Bambino 2004	Orale	Aperto	Rush/lento	Latte	100	10
7	Meglio, Allergy 2004	Orale	Aperto	Lento	Latte	62	14,2
8	Enrique, JACI 2005	SLIT/sputata	RCT	Rush	Nocciola	45,4	64,6
9	De Boissieu, Allergynot 2006	SLIT	Aperto	Lento e sub massim	Latte (1 ml)	12,5	50
10	Buchanan E, JACI 2007	Orale	Aperto	Rush/lento	Uovo	100	43
11	Morisset, A Ann Clin Immunol 2007	Orale	RCT (SBPCFC)	Lento	Latte/uoovo	?	11,1
12	Staden U, Allergy 2007	Orale	RCT	Lento	Latte/uoovo	100	36
13	Zapatero, JACI 2008	Orale	Aperto	Lento	Latte	68,5	11,4
14	Longo, JACI 2008	Orale	RCT	Rush/lento	Latte	100	10
15	Staden, JACI 2008	Orale	Aperto	Rush	Latte (120 ml)	100	33,3
16	Skripak, JACI 2008	Orale	RCT-DB	Lento	Latte (15 ml)	35	23
17	Fernandez Rivas, Allergy 2009	SLIT/deglutita	RCT	Rush/lento e submas	Pesca (Pru P3)	100	3
18	Caminiti L, Allergy Asth Proc 2009	Orale	RCT (in parte)	Lento	Latte	80	20
19	Hofman AM, JACI 2009	Orale	Aperto	Rush/lento	Arachidi	93	7
20	Jones SM, JACI 2009	Orale	Aperto	Rush/lento	Arachidi	38	7
21	Blumchen K, JACI 2010	Orale	Aperto	Rush/lento	Arachidi	-	100/36,4
22	Pajno G , AAAI 2010	Orale	SDPCFC	A settimane	Latte	77	15
23	Kaneko H, IJACI 2010	Orale	Aperto	Lento	Latte	50	20
24	Garcia Rodriguez, JACI 2011	Orale	Aperto	Rush/lento	Uovo	78,3	13,1
25	Anagnostou K, CI Exp All 2011	Orale	Aperto	Lento	Arachidi	86	14
26	Martorell A, CI Exp All 2011	Orale	RCT	Lento	Latte	80	10
27	Varshney P, JACI 2011	Orale	RCT-DB	Rush/lento	Arachidi	-	16
28	Keet CA, JACI 2011	Orale/SLIT	RCT	Lento	Latte	-	-
29	Ojeda P, JMAI 2012	Orale	Aperto	Lento	Uovo	74,2	16,1
30	Garcia S, JMAI 2012	Orale	Aperto	Lento	Latte	70,5	19.1 (incl drop out)
31	Tortajada Girbes M, JIACI 2012	Orale	Aperto	Lento	Uovo	≥ 62,5	10,5

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■ the acquisition of tolerance in eggallergic
■ children: a 5-yr follow-up.
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■ egg allergy: hypothesis-generating observations. *J Allergy Clin Immunol*
■ 2008; 122:414–415.

Boyano-Martinez T, Garcia-Ara C, Az-
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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

- Inserire l'articolo di shek e savage

ITER DIAGNOSTICO DELLE ALLERGIE ALIMENTARI

ANAMNESI

DIETA DI
ELIMINAZIONE

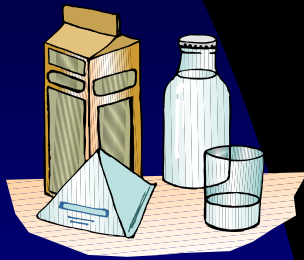
ESAMI DI LABORATORIO
(Prick test, "RAST", Patch test, etc.)

Diagnostica molecolare?

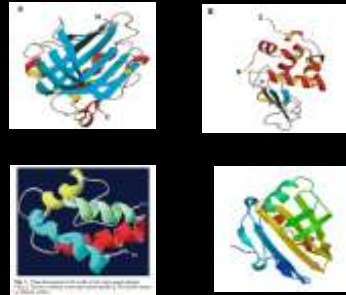
TEST DI SCATENAMENTO

Premessa

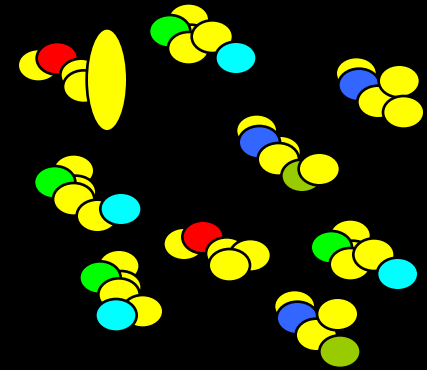
Estratti



Molecole

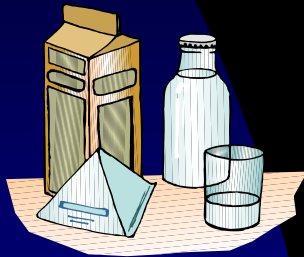


Epitopi

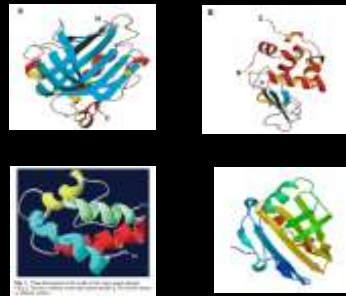


Premessa

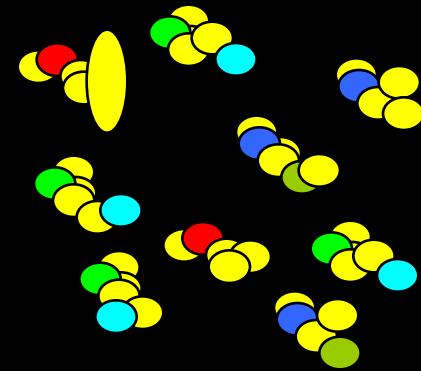
Allergico al
latte



Allergico alle
molecole del latte



Allergico agli
epitopi del latte

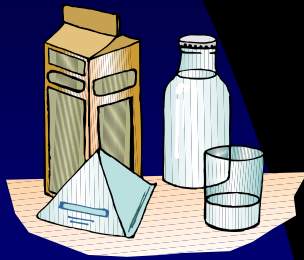


Nel latte vaccino vi
sono oltre 40 proteine
e tutte possono indurre
una risposta
immunologica

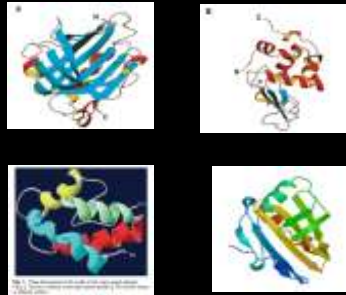
La Beta-lattoglobulina contiene diversi epitopi, riconosciuti dalla gran parte dei sieri, corrispondenti a sequenze brevi (i frammenti 41-60, 102-124, 149-162) altri riconosciuti solo dal 50-60% degli allergici (1-8, 25-40, 92-100) altri ancora solo dal 30-40% (78-83, 125-135) probabilmente conformazionali.

Premessa

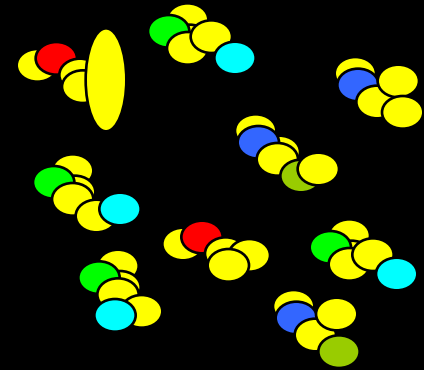
Estratti



Molecole



Epitopi



Maggiore complessità nella interpretazione delle risposte

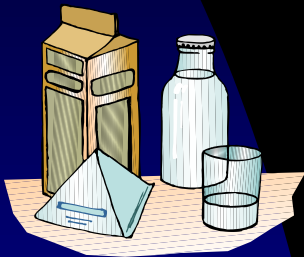
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10?

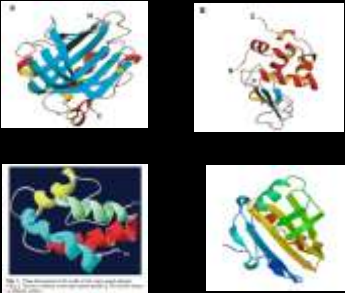
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Premessa

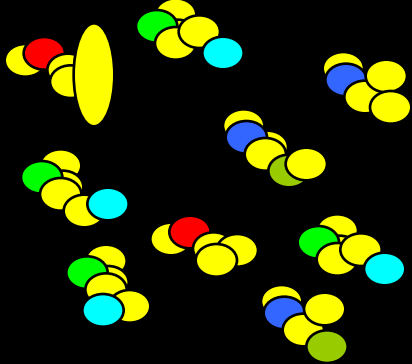
Estratti



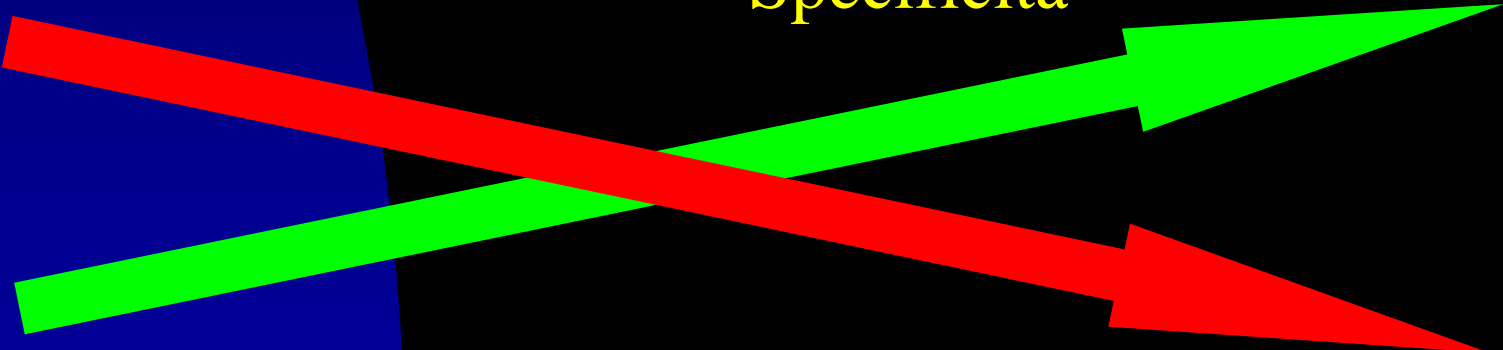
Molecole



Epitopi



Specificità



Sensibilità

RIAP

immunologia pediatrica
rivista allergologia



Organo Ufficiale della Società Italiana di Allergologia ed Immunologia Pediatrica

Supplemento 3

05

ottobre 2009 • anno XIII

Come si dovrebbe fare e valutare il Test di provocazione orale per alimenti

Norme pratiche di comportamento

Commissione Allergie Alimentari, Anafilassi e Dermatite Allergica della SIAIP

Commissione Diagnostica Allergologica della SIAIP



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In pratica nella gran parte dei bambini con sospetta allergia alimentare, il test di provocazione orale (TPO) per alimenti o test di scatenamento o, con termine inglese, il “challenge”, è l’unico test in grado di confermare in via definitiva la diagnosi di allergia alimentare.

Il TPO è tuttavia un test complicato, che impegna sia il medico sia la famiglia, e non è scevro da rischi per il paziente. Sebbene sia considerato da anni il gold standard nella diagnosi delle allergie alimentari, presenta ancora molti punti controversi ...

Diagnosi Molecolare

ImmunoCAP (Phadia)

ImmunoCAP ISAC

Tante molecole
non significa
tutte le molecole

Elevata sensibilità
Compatibilità con estratti
(procedura a due fasi)
Singleplex, diagnosi mirata
Accessibilità
Volume = 50 μ l per molecola

112 molecole
Test semi-quantitativi
Discreta riproducibilità
Incompatibilità con estratti
Pannello rigido
Volume = 20 ml per 112 molecole

<u>Code</u>	<u>Name</u>	<u>Latin name</u>
<u>f430</u>	<u>rAct d 8 PR-10, Kiwi</u>	<u>Actinidia deliciosa</u>
<u>f417</u>	<u>rApi g 1.01 PR-10, Celery</u>	<u>Apium graveolens</u>
<u>f422</u>	<u>rAra h 1 Peanut</u>	<u>Arachis hypogaea</u>
<u>f423</u>	<u>rAra h 2 Peanut</u>	<u>Arachis hypogaea</u>
<u>f424</u>	<u>rAra h 3 Peanut</u>	<u>Arachis hypogaea</u>
<u>f352</u>	<u>rAra h 8 PR-</u>	<u>Arachis hypogaea</u>
<u>f427</u>	<u>rAra h 9 LTP, Peanut</u>	<u>Arachis hypogaea</u>
<u>f354</u>	<u>rBer e 1 Brazil nut</u>	<u>Bertholletia excelsa</u>
<u>f428</u>	<u>rCor a 1 PR-10, Hazel nut</u>	<u>Corylus avellana</u>
<u>f425</u>	<u>rCor a 8 LTP, Hazel nut</u>	<u>Corylus avellana</u>
<u>f353</u>	<u>rGly m 4 PR-10, Soy</u>	<u>Glycine max</u>
<u>f419</u>	<u>rPru p 1 PR-10, Peach</u>	<u>Prunus persica</u>
<u>f420</u>	<u>rPru p 3 LTP, Peach</u>	<u>Prunus persica</u>
<u>f421</u>	<u>rPru p 4 Profilin, Peach</u>	<u>Prunus persica</u>
<u>f416</u>	<u>rTri a 19 Omega-5 Gliadin, Wheat</u>	<u>From Triticum aestivum</u>

.. 1 nel kiwi, nel sedano, nella soia e nel grano, 5 nella arachide, 2 nella nocciola e 3 nella pesca).

Oral food challenges in children are safe and severe reactions are almost all due to respiratory symptoms.

..the great majority of children with positive challenge developed only mild reactions. About one third of patients developed generalized reactions, more frequently involving the skin and the gastrointestinal system, and in half of the cases the upper respiratory tract system. No patients had cardiovascular symptoms. Severe or potentially severe reactions were all localized to the respiratory tract: lower respiratory (n. 6) or laryngeal involvement (n. 5) developed in 11/254 (4.3%) OFCs.

Table 2 Demographics of subjects of 254 positive OFCs in relation to severity of reaction

	Mild N = 167 (65.7%)	Multi-organ N = 81 (31.9%)	Anaphylaxis N = 6 (2.4%)	P value
Age (yr) median (interquartile range)	4 (2 – 6)	4 (3 – 6)	7 (5 – 8)	0.03
Male sex	115 (67.6)	53 (31.2)	2 (1.2)	0.1
DBPCFC (N)	24 (64.9)	13 (35.1)	0	0.4
<i>Food</i>				
Egg	75 (61)	45 (36.6)	3 (2.4)	0.2 #
Milk	54 (65.1)	26 (31.3)	3 (3.6)	0.6 #
Wheat	12 (80)	3 (20)	0	0.4 #
Other foods	26 (78.8)	7 (21.2)	0	0.1 #
<i>System</i>				
Skin	120 (71.9)	65 (79.3)	5 (83.3)	0.1 *
Gastrointestinal	46 (27.7)	69 (85.2)	5 (83.3)	< 0.001*
Respiratory	14 (8.4)	48 (59.3)	8 (100)	< 0.001*
Cardiovascular	0 (0)	0 (0)	0 (0)	Ns *

Statistical difference is assessed between severity of reaction to the food in question and all other foods.

* chi for trend

UOVO DI GALLINA

l'*ovomucoide* (Gal d 1)^[i] maggiormente presente nell'albume^[ii], è il maggiore allergene dell'uovo. Resiste al calore e agli enzimi acidi e proteolitici secreti durante la digestione

l'*ovalbumina* (Gal d2)⁷ è la seconda tra le proteine allergizzanti dell'albume anch'essa abbastanza termostabile e resistente agli agenti acidi.

l'*ovotransferrina* (Gal d III)⁷ o conalbumina, è la seconda proteina

il *lisozima* (Gal d IV)⁷ viene usato da alcune popolazioni come conservante^[xi] ed in Europa lo si aggiunge come additivo a farmaci e ad alcuni formaggi a pasta dura per prevenire la formazione di colonie batteriche

l'*α-livetina* (Gal d V)⁷ o *siero albumina del pollo*, presente nel tuorlo e nella carne del pollo, perde solo parzialmente il suo potere allergizzante se sottoposta a cottura; è responsabile della cross-reattività tra la carne del pollo e la forfora degli uccelli domestici



Un uovo di piccole dimensioni è costituito da

tuorlo	17 g = 29,8%
albume	33 g = 57,9%
parte non edibile	7 g = 12,3%

% Uovo intero	% Acqua	% Proteine	% Lipidi	% Glucidi	% Minerali	Kcal	
Guscio	8,5-10,5	1	4	-	-	95	-
Albume	60-66	87-89	10,7	-	0,4-0,5	0,5-0,7	43
Tuorlo	24-30	46,5-48,5	15,8	29,1	0,15-0,25	1,1-1,6	325
Albume + Tuorlo	90-92	74-76	12,4	8,7	0,3-0,4	0,8-1	128

Il tuorlo è costituito dal 16% di proteine e dal 32% di lipidi

Le proteine del tuorlo sono principalmente

- 1) Livetina
- 2) Fosvitina
- 3) Vitellina
- 4) vitellinina