Approccio al bambino con allergia alimentare

A. Fiocchi, Roma

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

34

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Presidenti: Prof. Nicola Principi - Prof.ssa Susanna Esposito

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Alessandro Fiocchi

UOC Allergologia
OPBG

Milano, 11 novembre 2014









Miti e realtà: Le allergie alimentari.

Alessandro Fiocchi

UOC Allergologia
OPBG

Roma, 28 ottobre 2014

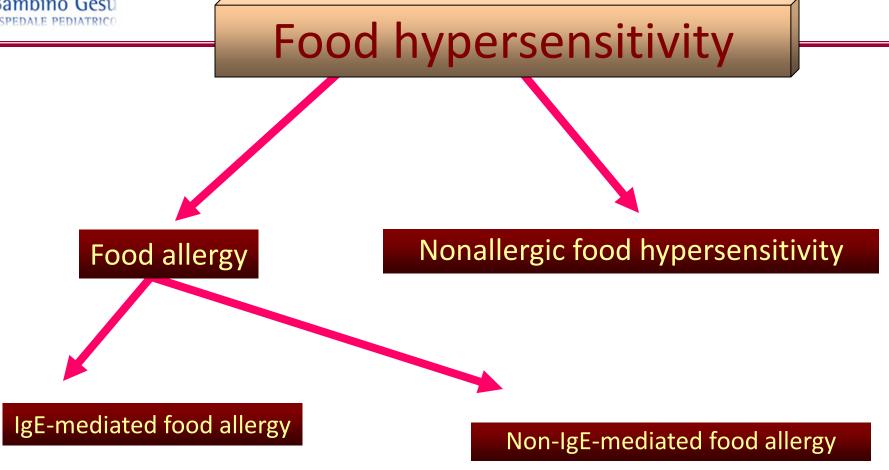


1. Il bambino con pretesa allergia alimentare

- 2. Il bambino con allergia alimentare non IgE-mediata
 - 3. Il bambino con allergia severa ad un alimento
 - 4. Il bambino con allergia severa a più alimenti

5. Conclusioni





Johansson SGO. Revised nomenclature for allergy for global use:

Report of the Nomenclature of WAO

J Allergy Clin Immunol 2004; 113; 832-6



Respiratory symptoms

Symptom-based Clinical Score (Cow's Milk Protein Intolerance Score)

| Symptom | Score |
|------------------------------|--|
| Crying* | 0 <1 hour/day |
| • • | 1 1-1.5 hours/day |
| | 2 1.5-2 hours/day |
| | 3 2 to 3 hours/day |
| | 4 3 to 4 hours/day |
| | 10. Vandenplas Y, Steenhout P, Planoudis Y, Grathwohl D; |
| Regurgitation [†] | Althera Study Group Treating cow's milk protein al- |
| | lergy: a double-blind randomized trial comparing two |
| | extensively hydrolysed formulas with probiotics. Acta |
| Stools | Paediatr 2013;102:990-8. |
| (Bristol scale) [†] | 11. Vandenplas Y, Althera Study Group Steenhout P, |
| Skin symptoms | Grathwohl D. A pilot study on the application of a symp- |
| omi symptoms | tom-based score for the diagnosis of cow's milk protein |
| | allergy. SAGE Open Med 2014; 2:205031211452 3423. |
| | Severe 3 3 |
| | 0 or 6 Urticaria (no 0/yes 6) |

No respiratory symptoms

Slight symptoms

Mild symptoms Severe symptoms Vandenplas Y.
Treatment of Cow's
Milk Protein Allergy.
Pediatr Gastroenterol
Hepatol Nutr.
2014;17:1-5

^{*}Crying was only considered if the child was crying for 1 week or more, assessed by the parents, without any other obvious cause.

†Vandenplas Y, Hachimi-Idrissi S, Casteels A, Mahler T, Loeb H. A clinical trial with an "anti-regurgitation" formula. Bur J Pediatr 1994;153:419-23.

[†]Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920-4.

Domenica 25 Marzo 2012 Corriere della Sera

Questi prodotti devono essere sempre citati I nelle etichette del prodotti che il contengono

Arachide

Cronache

Barletta La vittima aveva 29 anni. Due donne salvate dall'antidoto

Test anti allergie da eBay Muore nel centro clinico

Medicina forse contaminata, controlli in tutta Europa

Il commento

QUEI FARMACI IN RETE SENZA CONTROLLI

di ADRIANA BAZZI

a vicenda di Barletta (una donna morta dopo un esame per le intolleranze osservazione) è complicata e pone almeno tre tipi di problemi. Primo: l'utilizzo di medicinali comperati su eBay (in questo caso il sorbitolo che, usato per il test, doveva dimostrare l'incapacità dell'intestino di assorbire certi cibi e spiegare certi sintomi del paziente, come il gonfiore intestinale, il sovrappeso, la cefalea e via dicendo). Il commercio di medicine via Internet è senza controllo: al top della classifica ci sono i farmaci Viagra-simile, contro l'impotenza sessuale, che di solito sono acquistati da cittadini comuni, ma, a quanto pare, anche i medici privati (per risparmiare?) comprano prodotti farmaceutici (il sorbitolo) da utilizzare nei loro ambulatori, senza prove di sicurezza. Secondo: i centri privati

dovrebbero garantire la qualità delle loro

DAL NOSTRO INVIATO

BARLETTA - Cinque grammi. Solo cinque. Di una sostanza innocua. Ma acquistata via internet su eBay da una partita probabilmenté contaminata da un veleno potentissimo. Che ora si cerca, in tutta Europa, di fermare prima che possa uccidere ancora. Sperando che, come si sospetta, non lo abbia già fatto. Teresa Sunno, ventinovenne di Andria, residente a Trani, è morta così. In dieci minuti. Dopo aver bevuto quella sostanza, somministratale dal suo gastroenterologo privato alla ricerca di intolleranze alimentari. Non ha avuto il tempo nemmeno di arrivare al pronto soccorso, Teresa. Dove invece sono state salvate per un soffio Ar scia di 40 anni 6 Addolorata Piazzolla, di 62, ne avevano ingerito la stessa ostanza e in pochi minuti har o avuto un collasso. Vive grane a una fiala blu che Cosimo Sannito, responsabile del Prento soccorso mostra orgoglic riusciti tempestivamente a in-

dividuare l'antidoto e a som-



Giovane La vittima di ieri a Barletta: Teresa Sunno, 29 anni. originaria di Andria. Salve per un soffio altre due donne

lo, vi siano nitrati fortemente tossici. A Rovigo si indaga su un altro laboratorio che com-

mercializzava la stessa sostanza. Un'operazione capillare seguita passo passo dal ministro della Salute, Renato Balduzzi, Che ieri ha portato ad un primo risultato: ci sono altre situazioni sospette.

Allergie e intolleranze alimentari

Il capo della Procura di Trani, competente delle indagini, Carlo Maria Capristo, raccondo cautela: «Non dobbiamo sparge e il panico. Sono in corso tes specialistici sulla tossicità el farmaco. Sono analisi ap rofondite. Occorre un po' di empo e un po' di prudenza Forse ne doveva il medico ad acquiavere di pi maco online. Dove sicuramente si può risparmia-

re. Ma si trovano, sempre più

possa essere stato originariamente prodotto lì. Ora il medico, Ruggero Spinazzola, rischia un'accusa di omicidio colposo, lesioni gravi e avvelenamento colposo di sostanze alimentari. Ma si approfondisce anche la posizione del dottor Pappagallo, medico associato in quello studio clinico, cui si era rivolta la ragazza.

Altra frutta secca con quecio

Altri cereali Altri peaci

Altri crostacei

Aftre rosacee

Altri frutti

«Aveva un po' di acidità di stomaco» racconta Giovanni,

Dalla Gran Bretagna

La sostanza prodotta in Gran Bretagna, Sotto sequestro il centro che cura le intolleranze

gnata agli accertamenti e ora non si dà pace. «Teresa è stata sottoposta prima a una gastroscopia e poi a una colonscopia su consiglio del dottor Pappagallo, che la mandava però allo studio Spinazzola a Barletta». E non era sempre andata bene. Lo racconta il ragazzo: «Dopo alcune analisi, ha ritenuto di farla sottoporre a test per le intolleranze alimentari. Il primo lo ha fatto due settimane fa per verificare l'intolleranza al lattosio: è stata male tutto il giorno dopo averlo fatto. Il secondo era oggi (ieri, ndr). Si è sentita male, ma non è stata l'unica. Solo che lei poi è morta». Non consola, ma grazie all'allerta lanciato la morte di Teresa potrebbe non essere

CONCRETE DE LA MENA

Virginia Piccolillo

stata inutile.

La sostanza

Sorbitolo

Il sorbitolo è uno zucchero semplice, contenuto in frutti come mele, pere, susine, ciliegie e in quelli del sorbo (da cui deriva proprio il nome sorbitolo). Secondo alcune approfondite ricerche scientifiche la sostanza può essere intestinale, con la comparsa di sintomi diversissimi che vanno dal gonfiore di pancia, ai dolori addominali, alla stanchezza, fino al mal di testa. Il test al sorbitolo viene utilizzato per diagnosticare questi disturbi. Il suo uso è,

bambini di età inferiore a un anno di vita

Risparmi

prestazioni (il Per risparmiare i

Spesso provenienti dalla Cina. Il test letale, si sospetta che

l'amico che l'aveva accompa-



Symptor ed to food

Haemorroids

SKIN: Acne, dermatitis, e

HEADACHES: various kind

EYE CONDITIONS: conjunctivities, e, in the periods of blurred vision

temporary refractive changes.

earing loss, Sections, inflammations, Menieres, sections, repeated

Bedwetting gina, high blood pressure, irregular heartbeat, low blood pressure, rapid pulse. constipation, diarrhoea, gall bladder pains, wind, gastric ulcer, gastro-intestinal n, haemorchoids, indigestion, mucous colitis, nausea, pains or cramps, spastic

ing.

nosebleeds, polinasal of the state of the st

WROLOGICAL: bedwe Body odour tion, frequent urination, painful or difficult urination. cle cramps, muscle weakness.

MENTAL-BEHAVIOURAL: and provide a strong depression (including a concentration, general fatigue, hallucinations, hyperal fatigue, bility, bility, learning disorders, minimal from dysfunction, nervousness, peril fatigue, bility, bility, bility, learning disorders, minimal from dysfunction, nervousness, peril fatigue, bility, b

Psoriasis

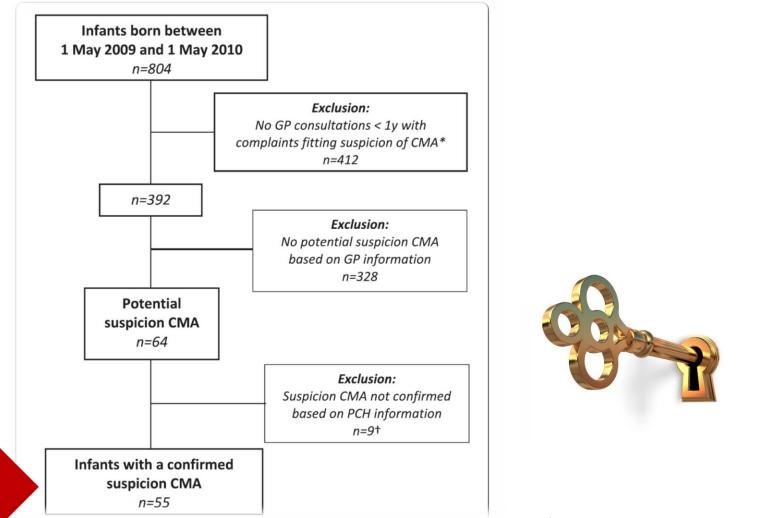
Refractive

changes

ring,

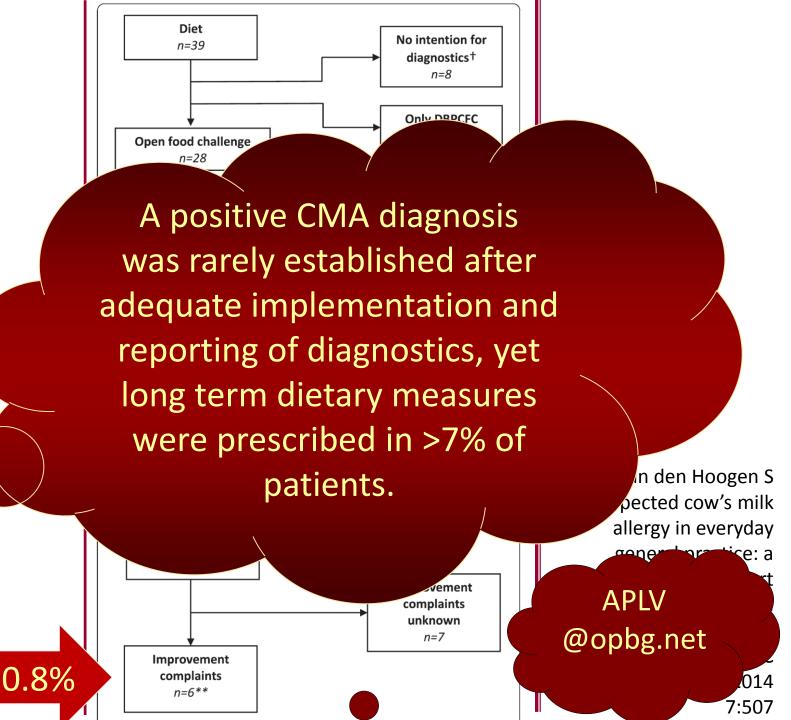


Unnecessary milk elimination diets in children with uncorrected diagnosis of CMA.

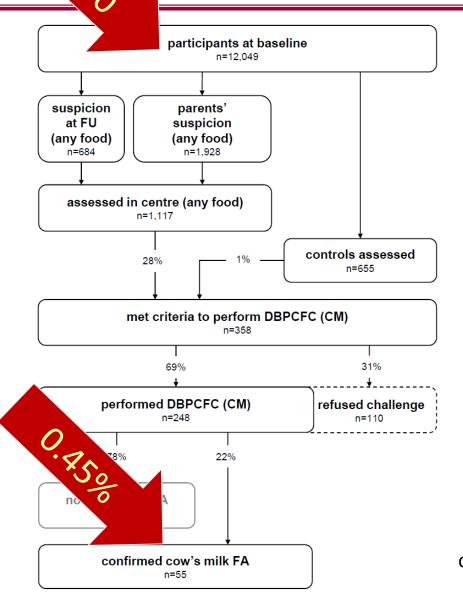


7%

van den Hoogen S.: Suspected cow's milk allergy in everyday general practice: a retrospective cohort study on health care burden and guideline adherence. BMC Research Notes 2014 7:507.



Unnecessary milk elimination diets in children with uncorrected diagnosis of CMA.





Schoemaker AA. Incidence and natural history of challenge-proven cow's milk allergy in European children - EuroPrevall birth cohort. Allergy. 2015;70:963-72



Nickel allergy. a diet regimen for diagnosis





Nickel allergy. Myth or reality? a narrative overview

Nickel is the leading cause of ACD (Allergic Contact Dermatitis). Systemic nickel allergy syndrome (SNAS) is very controversial. No challenge studies Nickel-related gastrointestinal symptoms Nickel-related chronic fatigue syndrome Nickel-related fibromyalgia Nickel-related headache Nickel-related recurring cold Nickel-related recurrent infections Nickel-related eczema

In the absence of genuine certainty, we can only conclude that further and broader studies, more rigorously conducted, are needed.

Pizzutelli S. Systemic nickel hypersensitivity and diet: myth or reality? Eur Ann Allergy Clin Immunol. 2011;43:5-18



9, AVENUE GERY 2" ÉTAGE 13500 LA CIOTAT TÉL: 34,42,63,41,18

LA CIOTAT, LE

REGIME SANS COBALT

SUPPRIMER LES ALIMENTS SUIVANT

haricots, betteraves, choux, abricots, noix,

fole,

pain complet,

clous de girofle,

café, thé, cacao, chocolats,

bière,









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Clinical symptoms of FPIES

| Mild – moderate acute FPIES | Severe acute FPIES | | | |
|---|--|--|--|--|
| Required | Required | | | |
| Vomiting (onset usually 1-3 hours, may range 30 minutes-6 hours): few episodes of intermittent vomiting (1-3), may be bilious | Vomiting (onset usually 1-3 hours, may range 30 minutes-6 hours): projectile (forceful), repetitive, bilious and dry heaving | | | |
| Decreased activity level | Altered behavior (from decreased activity to lethargy) | | | |
| • Pallor | • Pallor | | | |
| Self-resolving, the child is able to tolerate oral | Dehydration | | | |
| rehydration at home | Persistent, unable to rehydrate orally at home | | | |
| | | | | |
| Optional | Optional | | | |
| Mild watery diarrhea, onset usually within 24 hours, may be bloody (occasionally) | Hypotension | | | |
| | Abdominal distention | | | |
| | Hypothermia | | | |
| | Diarrhea, onset usually within 24 hours, may be bloody | | | |
| | | | | |

Nowak-Węgrzyn A. International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome. *Submitted*



Laboratory features of FPIES

| Mild – moderate acute FPIES | | Severe acute FPIES | | |
|-----------------------------|--|--------------------|---|--|
| • | Elevated white blood cell count with neutrophilia Thrombocytosis Stool may be positive for leukocytes, eosinophils or increased carbohydrate content | • | Elevated white blood cell count with neutrophilia Thrombocytosis Metabolic acidosis Methemoglobinemia Stool may be positive for leukocytes, eosinophils or increased carbohydrate content | |
| | | | | |

Nowak-Węgrzyn A. International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome. *Submitted*





Common food cross-reactivities/co-allergies in children with FPIES

| FPIES to | Clinical cross-reactivity/co-allergy | Observed Occurrence* |
|--------------------------|--------------------------------------|----------------------|
| Cow's milk | Soy | <30-40% |
| | Any solid food | <16% |
| Soy | Cow's Milk | <30-40% |
| | Any solid food | <16% |
| Solid food (any) | Another solid food | <44% |
| | Cow's milk or soy | <25% |
| Legumes* | Soy | <80% |
| Grains: rice, oats, etc* | Other grains (including rice) | about 50% |
| Poultry* | Other poultry | <40% |



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Avoiding milk, dairy products, and egg



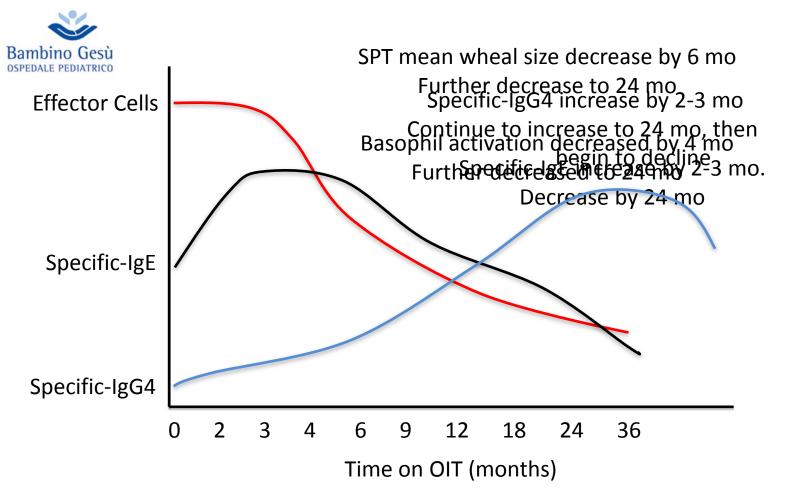


Food allergy immunotherapy goals

Goals of treatment are two-fold:

- Clinical desensitization tolerate more food on treatment than before starting
- 2. Eventual clinical tolerance off treatment can tolerate food –how long off treatment?

no good definition of tolerance —issue in all of allergic diseases "sustained unresponsiveness" —

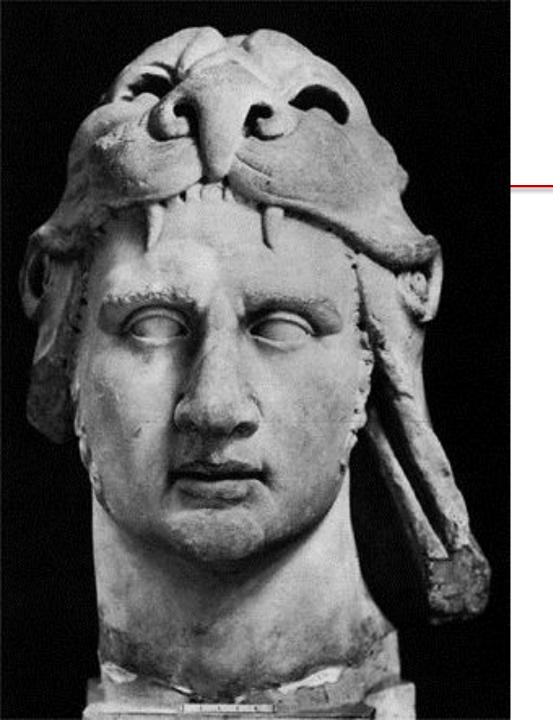


Skin prick: Jones et al, 2009; Blumchen et al, 2010; Varshney et al, 2011; Jones et al, 2011

Basophil activation: Jones et al, 2009; Jones et al, 2011

Specific IgE: Buchanan et al, 2007; Skripak et al, 2008; Longo et al, 2008; Jones et al, 2009; Blumchen et al, 2010; Varshney et al, 2011; Jones et al, 2011

Specific IgG4: Patriarca et al, 2003; Skripak et al, 2008; Jones et al, 2009; Blumchen et al, 2010; Varshney et al, 2011; Jones et al, 2011



Mithridates - King of Pontos (ancient Greece, now Turkey)
114-63 BC

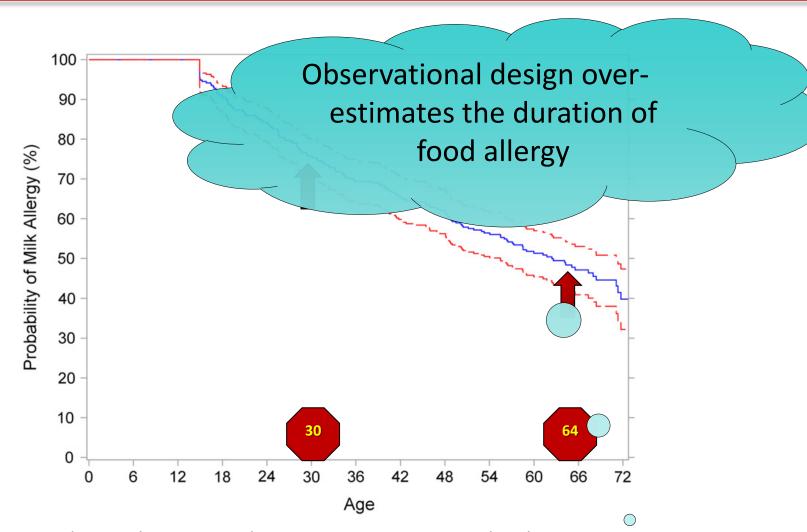
- lived in constant fear of being assassinated by the use of poison
 - so paranoid was he that he administered daily amounts of poisons in an attempt to make himself immune to as many poisons as he could.



- Large number of studies evaluated the ability for OIT to induce desensitization
- Few OIT studies have assessed for tolerance as a study outcome:
 - four uncontrolled open studies
 - three RCTs



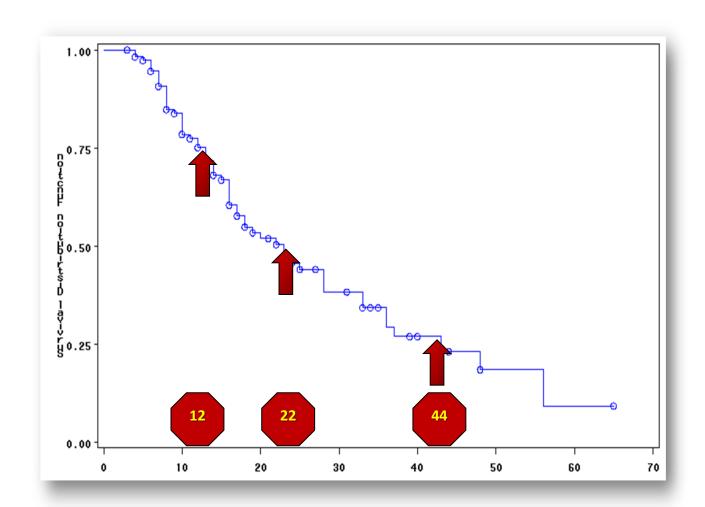
Natural history of milk allergy



Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, Henning AK, Mayer L, Burks AW, Grishin A, Stablein D, Sampson HA. The natural history of milk allergy in an observational cohort. J Allergy Clin Immunol. 2013;131:805-12



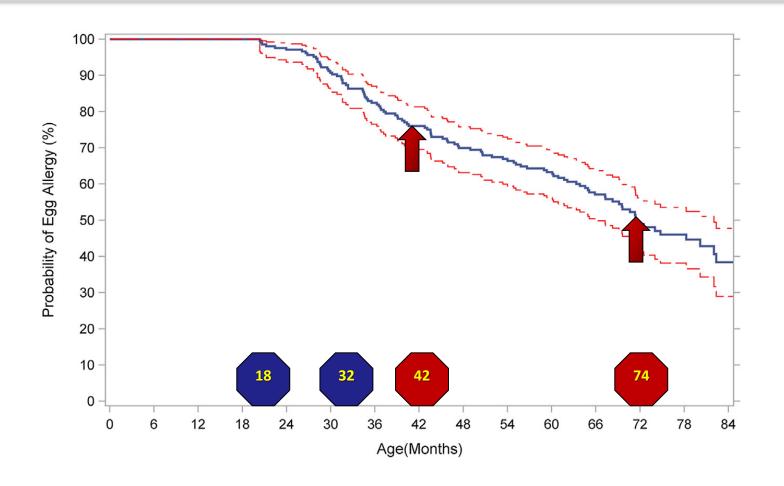
Natural history of milk allergy



Fiocchi A, Terracciano L Bouygue GR, Veglia F, Sarratud T, Martelli A, Restani P. Incremental prognostic factors associated with cow's milk allergy outcomes in infant and child referrals: the Milan Cow's Milk Allergy Cohort study. Ann Allergy Asthma Immunol 2008;101:166-73



Natural history of egg allergy

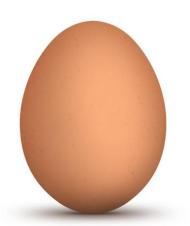


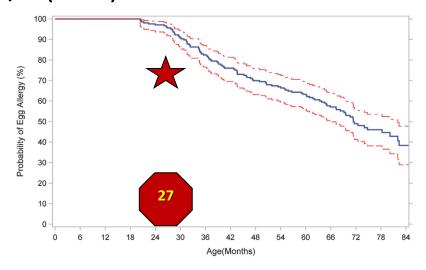
Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM, Dawson P, Mayer L, Burks AW, Grishin A, Stablein D, Sampson HA. The natural history of egg allergy in an observational cohort. J Allergy Clin Immunol. 2014;133:492-9



- open study
- 7 children with egg allergy
 - for two years
 - tolerance 2/7 (29%)

Buchanan ADI. Egg oral immunotherapy in nonanaphylactic children with egg allergy. J Allergy Clin Immunol 2007:119: 199–205





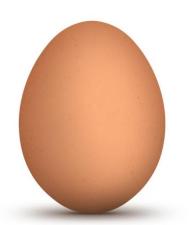
Sicherer SH. The natural history of egg allergy in an observational cohort.

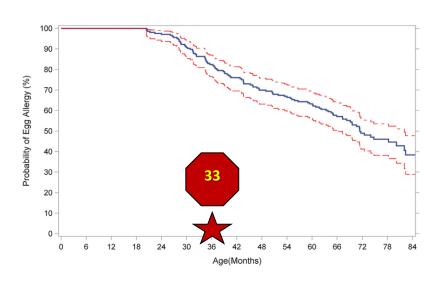
J Allergy Clin Immunol. 2014;133:492-9



- open study
- 6 children with egg allergy
 - for 33 months
 - tolerance 6/6 (100%)

Vickery BP, Pons L, Kulis MI. Individualized IgE-based dosing of egg oral immunotherapy and the development of tolerance. Ann Allergy Asthma Immunol 2010: 105: 444–50.





Sicherer SH. The natural history of egg allergy in an observational cohort.

J Allergy Clin Immunol. 2014;133:492-9



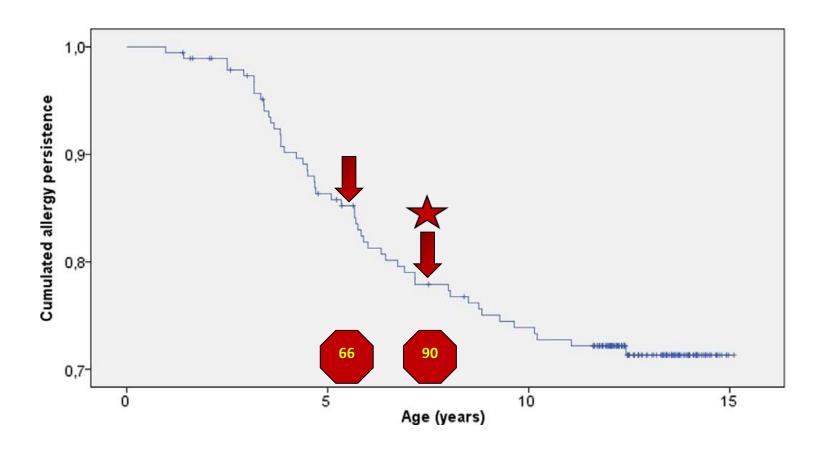
- Open study
- 23 children with peanut allergy
 - Median age 5.6 years
 - For 2 to 22 months
 - Tolerance 4/23 (17%)



Blumchen K, Ulbricht H, Staden U. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol 2011: 126: 83–91.



Peanut allergy natural history



Begin P. Natural resolution of peanut allergy: A 12-year longitudinal follow-up study.

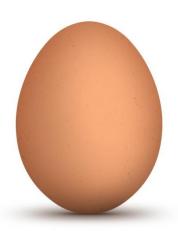
J Allergy Clin Immunol: In Practice 2013;1:528-30

Blumchen K, Ulbricht H, Staden U. Oral peanut immunotherapy in children with peanut

anaphylaxis. J Allergy Clin Immunol 2011: 126: 83-91.



- Open study
- 25 children with milk or egg allergy
- For 11 to 59 months
- Tolerance 9/25 (36%)
- Control group tolerated 35%





Staden U. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. Allergy. 2007;62:1261-9



| SOTI-group (n=25) | | | | |
|-------------------|------------------------------------|--------|--|--|
| Pattern | | N (%) | | |
| I | Responder (natural corse or SOTI?) | 9 (36) | | |
| II | Responder | 3 (12) | | |
| | (with regular daily intake) | | | |
| III | Partial responder | 4 (16) | | |
| IV | Non responder | 9 (36) | | |



| SOTI-group (n=25) | | | Control-group (n=20) | | |
|-------------------|---------------------------------------|--------|----------------------|---------|--|
| Pattern | | N (%) | Result | N (%) | |
| 1 | Responder (natural corse or SOTI?) | 9 (36) | Tolerant | 7 (35) | |
| II | Responder (with regular daily intake) | 3 (12) | | | |
| III | Partial responder | 4 (16) | | | |
| IV | Non responder | 9 (36) | Allergic | 13 (65) | |

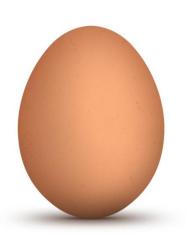




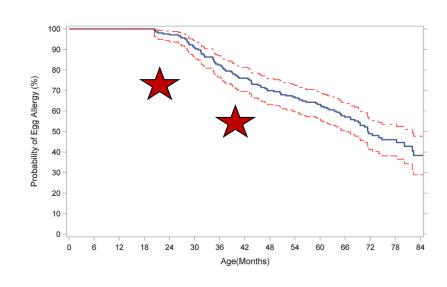
Burks AW, CoFAR. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med 2012;367:233-43



- RCT/Open study
- 40 children with egg allergy vs. 15 placebo
- For 22 months
- Tolerance 11/40 (28%)
- Control group lost

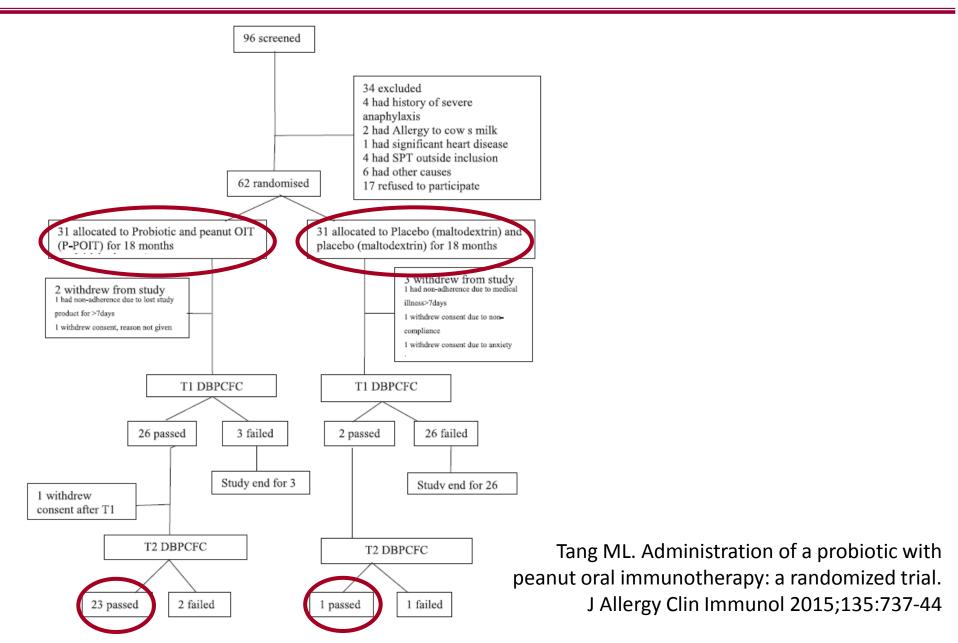


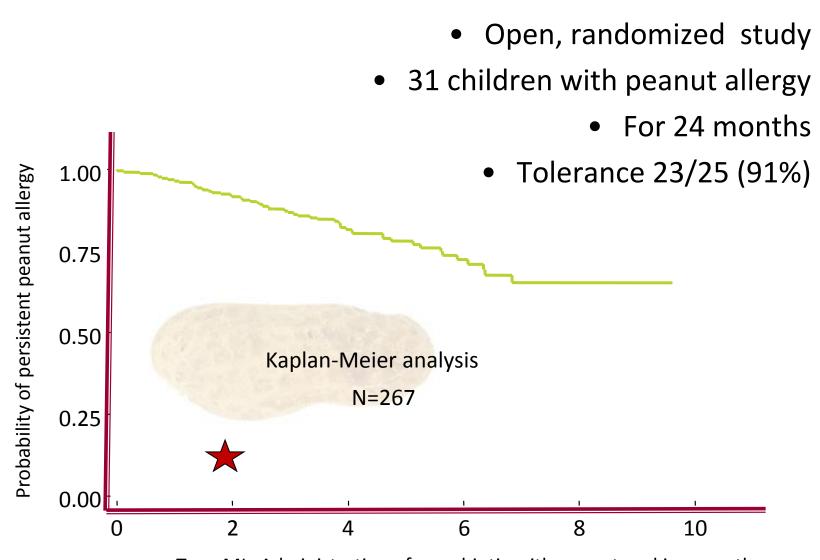




Burks AW. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med 2012: 367:233–43.



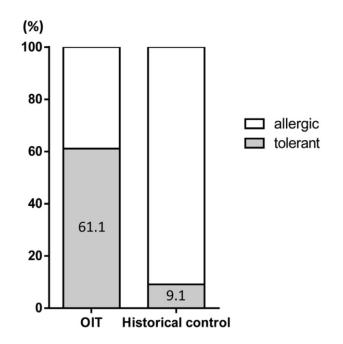


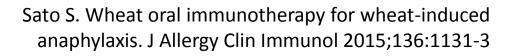


Tang ML. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol 2015;135:737-44



- Open study
- 18 children with wheat allergy
- For 24 months
- Tolerance 12/18 (60%)
- Control group impossible







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5. Conclusioni



The polyallergic child

Michele, 6.

Moderate persistent asthma

Minimal possible steroids dose [risk of arterial hypertension found in Misurina].

Food allergy with reactions to small doses of milk, egg, nuts, fresh fruit (kiwi, plum and apricot), fish, shrimp, soy, peanut.

Total IgE> 3000.



Uncontrolled asthma

- From 3 years of age
- one episode/month no seasonality
- desaturation during many ER accesses
- Fluticasone 125 x 2, LABA & MK (3-5 years)
- Betamethasone 5-10 times a year
- Misurina for three months
- Mites, grass, tree pollens, dog & cat hair.

Current therapy: Fluticasone, 250 mcg x 2 + MK 5 mg Childhood Asthma Control Test, **17**



Polysensitization

Total IgE 3027 kU / L

| sigE for foods, kUI/L | | | | slgE for inhalants, kUI/L | | | | |
|-----------------------|-------|---------|------|---------------------------|------|------------------|------|--|
| Egg white | > 100 | Shrimp | 64.8 | Grass | 19.4 | D. farinae | 11.1 | |
| Cow's milk | > 100 | Peanut | 28.9 | Corylus | 17.5 | D. pteronyssinus | 12.2 | |
| Hazelnut | > 100 | Soy | 25.7 | Birch | 15.8 | Dog dander | 17.9 | |
| Egg yolk | 91.3 | Chicken | 15.9 | Cupressus | 12.2 | Cat dander | 5.5 | |
| Cod | 88.1 | Beef | 6.30 | Olea | 7.9 | | | |



STAT-3 score

Total IgE 3027 kU / L

| | Points | | | | | | |
|------------------------------|--------|---|--------|-------|------------------|--|--|
| Clinical findings | 0 | 4 | Points | Scale | Scaled Points | | |
| Pneumonias (X-ray proven, #) | none | | 0 | 0.222 | 0 | | |
| Newborn rash | | X | 4 | 0.167 | 0.668 | | |
| Scoliosis, max curve | <10° | | 0 | 0.042 | 0 | | |
| Pathologic fractures | none | | 0 | 0.333 | 0 | | |
| Characteristic face | absent | | 0 | 0.333 | 0 | | |
| Gothic palate | absent | | 0 | 0.167 | 0 | | |



Food allergy - anaphylaxis

- Severe AD from the early months of life
- Immediate contact reactions to milk, egg.
- Inhalation reactions to milk, egg, fish.
- Hives and diarrhea immediately after apricot, kiwi, strawberry and plum.
- Hives and diarrhea hours after chicken and veal
- Immediate reactions after ingestion of fish, shellfish, nuts (hazelnuts, Brazil nuts), peanuts, lentils, soy.
- PedsQL 59.8 (parental) 67.8 (child) .



Michele. What now?...

- Oral Immunotherapy (OIT) has limits in multiple food allergy (MFA).
- Omalizumab is effective in severe asthma
- Omalizumab is contraindicated by serum IgE levels >1500 kUI/L
- Total plasma Exchange (TPE), anecdotally used to overcome this limit, reduces allergy symptoms per se

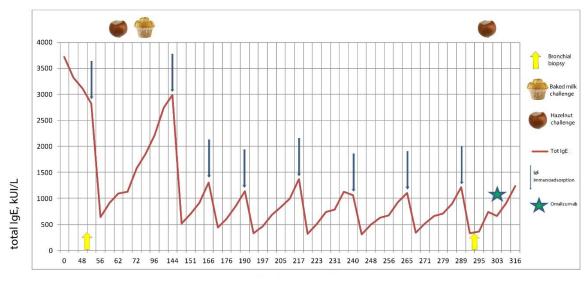


Michele. What now?...

- 10-days
- 1.5 plasma volume treated in eight aphaeresis sessions (2100 mL total plasma exchanged)
- mouse monoclonal anti-human IgE antibody coupled to Sepharose: Therasorb IgE, Miltenyi Biotec GmbH, Cologne, Germany.



Dahdah L. IgE Immunoadsorption knocks down the risk of foodrelated anaphylaxis. Pediatrics 2015; in press



time, hours



Michele. What now?...

- Asthma kept in control (score 25 one month after the 8th procedure)
- Montelukast withdrawn, Fluticasone tapered to 175 mcg/day
- Full tolerance to 1.5g baked milk protein (one muffin) after the first session
- Hazelnut tolerated up to 0.142g protein after the first session, 0.377g after the eighth, and 1.067g (full tolerance, 8 hazelnuts) after the first administration of Omalizumab.
- The boy became partially or fully tolerant to all the offending foods.
- PedsQL increased to 78.7 (parental) and 90 (child).



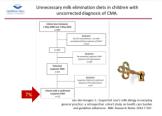
- 1. Il bambino con pretesa allergia alimentare
- 2. Il bambino con allergia alimentare non IgE-mediata
 - 3. Il bambino con allergia severa ad un alimento
 - 4. Il bambino con allergia severa a più alimenti

5. Conclusioni



Conclusion

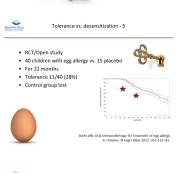
1. 'Food intolerance' may translate in overtreatment.



2. FPIES is increasing – it must be suspected



3. The immune mechanisms of tolerance may be little affected by OIT



4. Omalizumab is a possible solution

- 10-days

1.5 plasma volume treated in eight aphaeresis sessions (21 mL total plasma exchanged)

Michele. What now?..

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