Divezzamento ed allergia

Alessandro Fiocchi, Melloni Pediatria, Milano
Rattling the plate--reasons and rationales

Intelligent non-compliance?

Factors affecting the introduction of complementary foods in preterm infants.

Weaning age 17.1±0.23 weeks.

The introduction of complementary foods varied widely.

Compliance with guidelines was poor.

Further studies are necessary to see if weaning practices affect long-term growth and morbidity and to provide a basis for the development of appropriate recommendations.

Eur J Clin Nutr. 2002; 56:448-54
Basi del divezzamento come scienza

• 1. La evizione dei cibi solidi può influenzare lo sviluppo di allergia alimentare?
• 2. Quali gli alimenti più allergizzanti?
• 3. Si può stabilire una scala temporale di introduzione degli alimenti solidi?
1. La evizione dei cibi solidi può influenzare lo sviluppo di allergia alimentare?

• 135 bambini con familiarità allergica, alimentati al seno fino a 6 mesi

• **gruppo a (70)** - a 6 mesi: verdure cotte, mela, pera, cereali
  a 8 mesi: carne, pesce
  a 10 mesi: uovo

• **gruppo b (65)** - a 3 mesi: patata, carota cotta, cereali, carne
  a 4 mesi: uovo, pesce
  a 5 mesi: frutti diversi, "commercial foods"
  a 6 mesi: dieta libera ed estesa

→ sia eczema che allergia alimentare vennero riscontrati in misura maggiore nel gruppo b rispetto al gruppo a

1. La evizione dei cibi solidi può influenzare lo sviluppo di allergia alimentare?

- 279 lattanti ad alto rischio atopico vs. 80 lattanti con lo stesso rischio (non-intervention group)
- Incidenza di sintomi allergici: 1 anno (11.5 vs. 54.4%) a 2 anni (14.9 vs. 65.6%) a 3 anni (20.6 vs. 74.1%).
- Fattori più importanti nella patogenesi dei sintomi: (i) formula somministrata nella prima settimana di vita; (ii) divezzamento precoce (< 4 mesi); (iii) assunzione di manzo (< 6 mesi); (iv) introduzione precoce di latte vaccino (< 6 mesi); (v) fumo passivo e socializzazione precoce (< 2 anni di vita).

2. Quali gli alimenti più allergizzanti?

- Italia: uovo, latte, grano, pesce,
- USA: ++ Arachidi,
- Scandinavia: ++ Pesce,
- Giappone: ++ Soya, riso.

- La frequenza di sensibilizzazione varia con la cultura gastronomica, e riflette di regola la intensità e precocità dell'esposizione allergenica.
2. Quali gli alimenti più allergizzanti?

Allergenicità

• frequenza relativa con cui un alimento determina sensibilizzazione ed allergia in un gruppo di bambini atopici

• Fattori proponibili per calcolare un "indice di allergenicita" di ciascun alimento per ciascun bambino.

  • rischio di sensibilizzazione
    \[ = \frac{\% \text{ sensibilizzati}}{\% \text{ esposti}} \]
  
  • rischio di allergia
    \[ = \frac{\% \text{ allergici}}{\% \text{ sensibilizzati}} \]

  • rischio di persistenza allergia
    \[ = \frac{\% \text{ allergici dopo } x \text{ anni}}{\% \text{ allergici dopo } x \text{ anni}} \]

• rischio personale di allergia
  \[ = \text{ familiarità`} \]
Fish
Seafood
Egg and poultry
Legumes
Tree nuts
Seeds
Cereal Grains
Fruits and vegetables
ARBP
Cross-reactivity between fish species

Isolated allergy to a single species of fish:

- tropical sole
- swordfish

Positive skin test responses and clinical reactions to multiple fish in subjects with fish allergy

### Allergy to different fish species in cod-allergic children

<table>
<thead>
<tr>
<th>Species</th>
<th>SPT%</th>
<th>Clinical reaction% (history)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogfish</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Sole</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Tuna</td>
<td>55</td>
<td>35</td>
</tr>
<tr>
<td>Wrasse</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>Mackerel</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Anchovy</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Sardine</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Salmon</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

De Martino M.  
Allergy to different fish species in cod-allergic children: in vivo and in vitro studies.  
Allergy to different fish species in cod-allergic adults

- Eight adult patients
- History of reaction to codfish

<table>
<thead>
<tr>
<th>Species</th>
<th>Positive reaction</th>
<th>Tolerated</th>
<th>Never eaten</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaice</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Herring</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Mackerel</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Codfish</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Hansen TK.,
Codfish allergy in adults: IgE cross-reactivity among fish species.
Fish
Seafood
Egg and poultry
Legumes
Tree nuts
Seeds
Cereal Grains
Fruits and vegetables
Latex and fruits
ARBP
“Doctor, can I eat….”
Identification of tropomyosin

**Shrimp**
Daul CB. Identification of the major brown shrimp (*Penaeus aztecus*) allergen as the muscle protein tropomyosin.

**Crab**
Leung PS. Identification and molecular characterization of Charybdis feriatus tropomyosin, the major crab allergen.

**Lobster**
Leung PS. Molecular identification of the lobster muscle protein tropomyosin as a seafood allergen.

**Oyster, Scallop, Squid**
Leung PS. IgE reactivity against a cross-reactive allergen in crustacea and mollusca: evidence for tropomyosin as the common allergen.

**Anisakis**
Asturias JA. Is tropomyosin an allergen in Anisakis?

**Cockroach, grasshopper, dust mite**
Santos AB. Cockroach allergens and asthma in Brazil: identification of tropomyosin as a major allergen with potential cross-reactivity with mite and shrimp allergens.

van Ree R. Asthma after consumption of snails in house-dust-mite-allergic patients: a case of IgE cross-reactivity.
Allergy 1996;51:387-93.
Allergenicity of shellfish

16 patients with shrimp allergy: > 80% positive SPT to crab, crayfish, and lobster

   Daul CB. Immunologic evaluation of shrimp-allergic individuals.  

11 patients with shrimp allergy: the reaction to lobster, crab, and crayfish - 50% to 100%

   Waring NP. Hypersensitivity reactions to ingested crustacea: clinical evaluation and diagnostic studies in shrimp-sensitive individuals.  

Allergy to shrimp without allergy to other species

   Morgan JE. Species-specific shrimp allergens: RAST and RAST-inhibition studies.  
Why seafood has not to be introduced early

1. High risk for reactions to crustaceans
2. Reactions can be severe
3. Less common allergy to mollusks
4. IT with dust mite may be an additional risk factor
5. Determination of the precise risks requires further investigation

Sicherer SH. Clinical implications of cross-reactive food allergens
Fish
Seafood
Egg and poultry
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Seeds
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Fruits and vegetables
Latex and fruits
ARBP
“Doctor, can I eat....”
Bird-egg syndrome

alpha-livetin (feathers, egg, meat) indicated as sensitising protein

associated with reactions to chicken meat in 22% to 32%.

ausela BA. Peculiarities of egg allergy in children with bird protein sensitization.

zepfalusi Z. Egg yolk a-livetin (chicken serum albumin) is a cross-reactive allergen in the bird-egg syndrome.

the majority of children with egg allergy tolerate chicken
Cross-sensitisation between egg and meat from different avian species

- avian meat allergy uncommon
- cross-reaction to turkey, pheasant, and quail


- cross-sensitisation among various avian eggs common
- the clinical implications have not been systematically studied

Langland T.
Allergens in hen’s egg white from turkey, duck, goose, seagull, and in hen egg yolk, and hen and chicken sera and flesh. Allergy 1983;38:399-412.

Anibarro B, Seoane FJ, Vila C, Lombardero M.
Allergy to eggs from duck and goose without sensitization to hen egg proteins. Allergy Clin Immunol 2000;105:834-6.
Fish
Seafood
Egg and poultry
Legumes
Tree nuts
Seeds
Cereal Grains
Fruits and vegetables
Latex and fruits
ARBP
“Doctor, can I eat....”
# The leguminosae family

<table>
<thead>
<tr>
<th>Family</th>
<th>Subfamily</th>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leguminosae</td>
<td>Mimosoideae</td>
<td>Acacia</td>
<td>Arabic gum</td>
</tr>
<tr>
<td></td>
<td>Caesalpinoideae</td>
<td>Cassia</td>
<td>Senna</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceratonia</td>
<td>Carob bean</td>
</tr>
<tr>
<td></td>
<td>Papillionoideae</td>
<td>Glycyrrhiza</td>
<td>Liquorice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arachis</td>
<td>Peanut</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vicia</td>
<td>Broad bean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lens</td>
<td>Lentil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pisum</td>
<td>Pea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phaseolus</td>
<td>Beans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glycine</td>
<td>Soy bean</td>
</tr>
</tbody>
</table>
# Sensitisation in the leguminosae botanical family

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Tested at SPT</th>
<th>Positive</th>
<th>% positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>69</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>Soy</td>
<td>69</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>Pea</td>
<td>69</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Lima bean</td>
<td>41</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Green bean</td>
<td>32</td>
<td>13</td>
<td>41</td>
</tr>
</tbody>
</table>

Bernishel-Broadbent J, Sampson HA.  
Cross-allergenicity in the leguminosae botanical family in children with food hypersensitivity.  
## Soy allergy: fact or fiction?

<table>
<thead>
<tr>
<th>Allergen</th>
<th>SPT- positive</th>
<th>DBPCFC+</th>
<th>% false- positive SPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>60</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>Soy</td>
<td>30</td>
<td>10</td>
<td>67</td>
</tr>
<tr>
<td>Pea</td>
<td>18</td>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>Lima bean</td>
<td>9</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Green bean</td>
<td>13</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

### Soy allergy: fiction!

#### Challenge-based studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Setting</th>
<th>SPT+</th>
<th>DBPCFC+</th>
<th>False+ SPTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giampietro</td>
<td>Food allergy</td>
<td>22%</td>
<td>3%</td>
<td>86%</td>
</tr>
<tr>
<td>Bock</td>
<td>Food allergy</td>
<td></td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Sampson</td>
<td>AD</td>
<td></td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Magnolfi</td>
<td>AD</td>
<td>21%</td>
<td>0,85%</td>
<td>94%</td>
</tr>
</tbody>
</table>

## Allergy to other legumes among children allergic to peanut

<table>
<thead>
<tr>
<th>Reference</th>
<th>Legume</th>
<th>Number</th>
<th>SPT</th>
<th>RAST</th>
<th>Immunoblot</th>
<th>DBPCFC+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moneret-Vautrin</td>
<td>Lupine</td>
<td>24</td>
<td>11 (44%)</td>
<td>ND</td>
<td>ND</td>
<td>7/8 (87.5%)</td>
</tr>
<tr>
<td>Fiocchi</td>
<td>Carob</td>
<td>12</td>
<td>6 (50%)</td>
<td>3 (25%)</td>
<td>12 (100%)</td>
<td>None</td>
</tr>
</tbody>
</table>


Fiocchi A. Carob is not allergenic in peanut-allergic subjects. *Clin Exper Allergy* 1999;29:402-6
Legumes
Tree nuts
Seeds
Cereal Grains
Fruits and vegetables
Latex and fruits
ARBP

“Doctor, can I eat….”
Tree nuts

Severe clinical I reactions to tree nuts

Fatal or near-fatal reactions to tree nuts – also from a first exposure

High degree of IgE binding to multiple tree nuts

92% of 111 patients with peanut allergy, tree nut allergy, or both had IgE antibody to, and 37% had convincing reactions to more than one nut
Sicherer SH. Clinical implications of cross-reactive food allergens J Allergy Clin Immunol 2001;108:881-90
Allergenicity of tree nuts

No comprehensive studies

Extensive cross-reactions found:

Peanut – Nut – Brazil nut – Almond


Peanut – Nut


Pistachio-Cashew


→ caution is prudent! Total elimination of the nut family (perhaps with the exception of previously tolerated nuts eaten in isolation)

Hourihane JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. BMJ 1996;313:518-21
Legumes
Tree nuts
Seeds
Cereal Grains
Fruits and vegetables
Latex and fruits
ARBP
“Doctor, can I eat....”
Cross-reactivity between legumes, tree nuts, and seeds

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Co-sensitisation</th>
<th>%</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Hazelnut and Brazil nut</td>
<td>59</td>
<td>Hourihane 1996</td>
</tr>
<tr>
<td>Peanut</td>
<td>Tree nut</td>
<td>2.5 (self-report)</td>
<td>Sicherer 1999</td>
</tr>
<tr>
<td>Nuts</td>
<td>Sesame, poppy, mustard seed</td>
<td>Occasional reports</td>
<td>Rance, Asero</td>
</tr>
</tbody>
</table>

Legumes
Tree nuts
Seeds
Cereal Grains
Fruits and vegetables
Latex and fruits
ARBP
“Doctor, can I eat….”
Allergenicity of cereal grains

- Wheat, rye, barley, and oat share homologous proteins
- Cross-sensitisation with grass pollens
- High rate of cosensitization to these foods
- Low rate of clinical cross-reactivity at challenges
- Children with reactions to one grain are tolerant of all other grains in 80% of cases

Jones SM,.
Immunologic cross-reactivity among cereal grains and grasses in children with food hypersensitivity.

Donovan GR.
Crossreactivity of IgE antibodies from sera of subjects allergic to both ryegrass pollen and wheat endosperm proteins:evidence for common allergenic determinants.
Legumes
Tree nuts
Seeds
Cereal Grains
Fruits and vegetables
Latex and fruits

“Doctor, can I eat….”
The molecular basis of allergenicity

Pathogenesis-related proteins (PRs) - Glucanases, Chitinases, Thaumatin-like proteins, Bet v 1–homologous proteins, Lipid transfer proteins.

Inhibitors of proteases and amylases

2S albumins
Vicillins
Conglutinins
Thyol-proteases
Lectins

Oral allergy syndrome

isolated oral symptoms
labile proteins in fresh fruits and vegetables
homology with proteins in pollens

Kazemi-Shirazi L.
Quantitative IgE inhibition experiments with purified recombinant allergens indicate pollen-derived allergens as the sensitizing agents responsible for many forms of plant food allergy.

Valenta R.
Type 1 allergic reactions to plant-derived food: a consequence of primary sensitization to pollen allergens.
Allergenicity of fruits and vegetables

All fruits and vegetables can be allergenic


Clinical reactivity determined by DBPCFCs varies with the fruit (10% for pear and up to 90% for peach). Multiple fruit allergy common.

Cross-reactions between fruits and vegetables

Cross-reactivity between families - *e.g.* Rosaceae (peach, apple, apricot, almond, plum, pear, and strawberry).


Cross-reactivity across families: *e.g.* melon – watermelon – avocado – kiwi – chestnut – banana - peach

Pollen-fruit syndrome

Birch pollen - Rosaceae fruits
Ragweed – melon
Mugwort – celery

In general, low severity

Risk for severe reactions:
- fruit allergy develops without pollen allergy
- sensitisation to lipid transfer proteins (LTPs).
- systemic reactions occurred in 82% without compared with 45% with pollinosis


Adverse Reactions to Bovine Proteins

Annals of Allergy Asthma Immunology
December 2002; 89:6, Suppl 1
Goat’s and sheep’s milk

100% reactions at challenge in children with CMA
100% sensitisation at blotting in children with CMA

Goat’s milk

26 children with CMA
SPT with goat’s milk: 100% positive
Challenge with goat’s milk: 24/26 positive
Blotting cross-inhibition: 100%

Donkey’s milk

Tolerated by:

• children with severe gastrointestinal CMA
• children with “multiple food intolerance” allergic to eHF

Mare’s milk

17 children with CMA
SPT with mare’s milk: positive 1/17
Challenge with mare’s milk: positive 1/17
Blotting cross-inhibition: not relevant
Mare’s milk tolerated in 96% of children

Proteins in milk from different species

RAST in 28 children with BA

<table>
<thead>
<tr>
<th>Species</th>
<th>Proteins %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Human milk</td>
<td>1.03</td>
</tr>
<tr>
<td>Donkey</td>
<td>2.0</td>
</tr>
<tr>
<td>Mare</td>
<td>2.2</td>
</tr>
<tr>
<td>Cow</td>
<td>3.3</td>
</tr>
<tr>
<td>Goat</td>
<td>3.7</td>
</tr>
<tr>
<td>Sheep</td>
<td>5.3</td>
</tr>
</tbody>
</table>
## Prevalence (%) of adverse reaction to beef in children with CMA

<table>
<thead>
<tr>
<th></th>
<th>Gerrard</th>
<th>Sampson</th>
<th>Bishop</th>
<th>Høst</th>
<th>Werfel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>150</td>
<td>15</td>
<td>96</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>&gt;10y</td>
<td>Not specified</td>
<td>5y</td>
<td>36 mo</td>
<td>Not specified</td>
</tr>
<tr>
<td><strong>ARB</strong></td>
<td>7 (4.6%)</td>
<td>2 (13.3%)</td>
<td>14 (14.5%)</td>
<td>1 (4.7%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Open challenge</td>
<td>Parent report</td>
<td></td>
<td>DBPCFC +ve</td>
<td></td>
</tr>
</tbody>
</table>


Høst A. A prospective study of cow milk allergy in Danish infants during the first three years of life. *Allergy* 1990;45:587-96.

### SPT in 28 children with BA

<table>
<thead>
<tr>
<th></th>
<th>cBeef</th>
<th>fBeef</th>
<th>BSA</th>
<th>cMilk</th>
<th>fMilk</th>
<th>Casein</th>
</tr>
</thead>
</table>

Martelli A  
Allergy to cow’s milk in beef-allergic children.  
*Ann Allergy Asthma Immunol.* 2002; 89S, 25-33
Specific IgE in 28 children with BA

<table>
<thead>
<tr>
<th></th>
<th>Beef</th>
<th>Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP +ve</td>
<td>26/28</td>
<td>23/28</td>
</tr>
</tbody>
</table>

Cut-off point: 5 kU/L (beef)
18 kU/L (milk)

Martelli A
Allergy to cow’s milk in beef-allergic children.
*Ann Allergy Asthma Immunol.* 2002; 89S, 25-33
CMA in 28 children with BA

<table>
<thead>
<tr>
<th>DBPCFC</th>
<th>Beef</th>
<th>Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28/28</td>
<td>26/28</td>
</tr>
</tbody>
</table>

Martelli A
Allergy to cow’s milk in beef-allergic children.
*Ann Allergy Asthma Immunol.* 2002; 89S, 25-33
Persistenza delle allergie alimentari

- La "sopravvivenza media" di una diagnosi di allergia alimentare è del 71% a 3 anni, del 50% a 6 anni e del 28% a 9 anni.

- Uno stato di tolleranza viene raggiunto nella maggior parte dei bambini per il latte a 3 anni, per l'uovo a 7 anni, mentre molti altri alimenti possono determinare allergie di durata indefinita: e il caso del pesce, della soia, dell'arachide e dei crostacei.

Kjellmann NJM, Natural history and prevention of food allergy. Food Allergy 325, 1991
Fattori negativi per l’acquisizione di tolleranza

- alta età alla diagnosi
- lunga durata dei sintomi
- alto diametro del pomfo
- presenza di più di una manifestazione allergica
- noncompliance alla dieta di esclusione
- allergia a crostacei, frutta secca, arachidi, pesce, frutti di mare

Raccomandazioni per il divezzamento bambino a rischio atopico

• Ritardare l’introduzione dei cibi solidi al 5°-6° mese
• Ritardare l’introduzione del latte vaccino al compimento del 1° anno
• Introdurre l’uovo al compimento del 2° anno di vita
• Introdurre pesce, arachidi e frutta secca al compimento del 3° anno di vita
• Preferire gli alimenti estremamente cotti

Sampson H.A Evaluation and Management of Patients with Adverse Food Reactions, in Bierman et al. Allergy, Asthma and Immunology from infancy to childhood, Saunders ed, 1997
Raccomandazioni per il divezzamento bambino normale

Evidence-based

oppure

Eminence-based?
Dal mito alla realtà

L’allergologia pediatrica
dall’arte alla scienza

Temi specifici di interesse pratico alla luce
della letteratura scientifica

Dalla buona scienza al piccolo paziente