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

Alessandro Fiocchi, Allergy Division, The Bambino Gesù Paediatric Hospital, Rome, Vatican City State

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Educational objectives

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

- Understand the rationale behind the use of different tests for the diagnosis of food allergy
- Identify the best way patient by patient
- Assess the impact of a correct diagnosis on treatment of food allergy

Conflict of interest

Speakers’ Bureau: none

Advisory boards: ALK-Abellò, Chiesi, Stallergènes Italy

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

Not all children reported have food allergy

1.7 self-reported
1.2 SPT+ve confirmed at DBPCFC

OFCC + history + SPT


NIH guidelines for the diagnosis and management of food allergy

Guideline 11: The EP recommends using oral food challenges for diagnosing food allergy. The double-blind placebo-controlled food challenge (DBPCFC) is the “gold standard” for clinical setting, whereas single-blind and open food challenges may be considered diagnostic when there are objective symptoms (i.e., negative challenge) that correlate with medical history and are supported by laboratory tests.


Oral food challenges

When
- Open, single-blind, double-blind?
- Preparing the patient
- Preparing the food
- Choosing the placebo
- Challenge administration
- Interpretation
- Repeating challenges
- Patient education
- Conclusions
Indications for food challenges

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

Benefits of food challenges

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

If negative:
- expansion of the diet
- improvement of the patient’s nutrition and quality of life.

Risks of food challenges

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

Risk assessment

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

Medium

Low

Can we perform OFC?

SPT? ImmunoCAP?

Yes

No

Question 1

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

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

(WoW)
If SPT positive:
unnecessary treatment of
1 in 20 patients
misclassified as CMA
(56% false positive results).

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

Question 1
Should skin prick tests be used for the diagnosis of IgE-mediated cow’s milk allergy (CMA) in patients suspected of CMA?

- Strong/Conditional Recommendation

If oral food challenge required for IgE-mediated allergy - do only food challenge and no other tests
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Strong/Conditional Recommendation Very low/Low quality evidence

How can I be sure that it’s milk?

False positive: 17–29%
False negative: 8–18%
Cut-off: 0.35 kUI/L
Properly done topical therapy for a reasonable period in moderate to severe atopic dermatitis (AD) resistant to presence and absence of CMA.

Clinical history of food protein ingestion (within 2 hours after ingestion) with positive CM IgE tests. Respiratory symptoms occurred immediately (within 2 hours after ingestion). Not indicated at diagnosis.

CMA anaphylaxis: not indicated at diagnosis. Verify every 12 months for assessment of tolerance onset. Open Hospital.

Generalized, important allergic reaction in a single organ (such as urticaria, angioedema, or vomiting, or respiratory symptoms) occurred immediately (within 2 hours after ingestion) with positive CM specific IgE tests. Not indicated at diagnosis. Verify every 3-12 months, depending on age, for assessment of tolerance onset. Open Hospital.

Clinical history of food protein enterocolitis from cow's milk with at least one previous episode, both in presence and absence of CMA-specific IgE. Not indicated at diagnosis. Verify every 18-24 months, for assessment of tolerance onset. Indicated DBPCFC Hospital.

Moderate to severe atopic dermatitis (AD) resistant to properly done topical therapy for a reasonable period in presence of IgE antibodies to CM.

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Clinical situation: Clinical situation not suggestive and/or clinical response not immediate (eg. EoE) when patient or her family are convinced of the existence of CMA and thus inclined to interpret any clinical signs as related to cow's milk ingestion.

First introduction of cow's milk in CM-sensitized children. Reintroduction of cow's milk excluded from the diet for several months on a mere detection of specific IgE in the absence of a suggestive clinical history.

Clinical subjective symptoms (nausea, abdominal pain, itching, oral etc.) after CM ingestion. Delayed allergic reaction (eczema, chronic diarrhea, colitis, allergic proctocolitis, gastroesophageal reflux) without CM-specific IgE. In the context of clinical studies.

Indicated DBPCFC Hospital.

Fiochi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow's Milk Allergy. The DRACMA guideline. WAO Journal 2010; 51 (April), 1-105.

Open or blinded? - I

<table>
<thead>
<tr>
<th>Clinical history</th>
<th>Indication</th>
<th>Challenge</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
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Preparation: stopping treatments before the procedure.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Last dose before OFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antihistamines</td>
<td>3-10 d</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>3 d</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>3 d</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>7-10 d</td>
</tr>
<tr>
<td>Loratadine</td>
<td>7 d</td>
</tr>
<tr>
<td>Antihistamine nose spray</td>
<td>12 h</td>
</tr>
<tr>
<td>Oral H2 receptor antagonist</td>
<td>12 h</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>3 d – 3 wk, drug-dependent</td>
</tr>
<tr>
<td>Oral/lm/lr steroids</td>
<td>3 d – 2 wk</td>
</tr>
<tr>
<td>Leukotriene antagonist</td>
<td>24 h</td>
</tr>
</tbody>
</table>

Preparation: stopping treatments before the procedure

May be continued:

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

Medication

**Last dose before OFC**

**Short-acting bronchodilator**
- Albuterol 8 h
- Terbutaline, isoproterenol, 24 h

**Long-acting bronchodilator 24 h**

**Inhaled cromolyn sodium 48 h**
- Nedocromil sodium 12 h

May be continued:

- Antihistamine eye drops
- Inhaled/intranasal corticosteroids
- Topical steroids
- Inhaled/intranasal corticosteroids
- Topical steroids

Venous access pre-challenge?

- Milk, wheat: sIgE > 17.5 kU/l
- Egg: sIgE > 3.5 kU/L


Food preparation: cooking does matter

When

- Open, single-blind, double-blind?

Preparing the patient

Preparing the food

Choosing the placebo

Challenge administration

Interpretation

Repeating challenges

Particular situations

Conclusions

Preparation: exclusion diet before challenge

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


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The ideal placebo

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


An ideal placebo

A dessert to blind celeriac and hazelnut

Triangle test

Sufficient blind processing

It can be reproducibly manufactured


Which placebo is used in the everyday milk challenge?


Oral food challenges

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Particular situations
Conclusions
Food challenges.
Initial dose.

<table>
<thead>
<tr>
<th>Food</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>0.1 mg</td>
</tr>
<tr>
<td>Cow’s milk</td>
<td>0.1 mL</td>
</tr>
<tr>
<td>Egg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Cod</td>
<td>5 mg</td>
</tr>
<tr>
<td>Wheat</td>
<td>100 mg</td>
</tr>
<tr>
<td>Soy</td>
<td>1 mg</td>
</tr>
<tr>
<td>Shrimp</td>
<td>5 mg</td>
</tr>
<tr>
<td>Nuts</td>
<td>0.1 mg</td>
</tr>
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</table>

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

Interval between doses

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


Further doses: three schemes

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

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

1014 DBPCFC (in order of rate of occurrence)

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

Presentation symptoms vs. reaction at challenge


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


Oral food challenges

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Natural history of nut allergy

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

Egg allergy: Is it forever?

Tolerance reached in:

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

García Ara MC. Therapeutic approach to and prognosis of food allergy. Allergol Immunopathol 1996;24(suppl 1):31-5

Repeating challenges: the MiCMAC flow-chart

Repeating challenges:

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


The Baltimore Cohort – survival curves

No challenge repetition

Longer milk avoidance

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

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Challenge through breastmilk

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


DBPCFEC

A 14-years-old boy
3 episodes of FDEIA following ingestion of meals containing:

a. unpealed sausage;
b. Mascarpone (an italian creamy cheese);
c. artichokes.

All resulted contaminated by molds
Pericilliun Lanoso-Cenuleum species (PLC) cultured in Agar

Challenges with PLC on separate days
DBPCFEC with PLC food exercise treadmill ergonometric 120 minutes after a meal containing artichokes, Mascarpone, and sausage
DBPCFEC 120 minutes after four similar meals with the double-blinded addition of doubling doses of PLC solution (0.5, 1, 2, 4 milliliters), or of the excipient as a placebo.


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