IgE- BASED ALLERGY- DIAGNOSTICS IN CHILDHOOD -

RECENT EAACI RECOMMENDATIONS -

WITH SPECIFIC ATTENTION TO FOOD ALLERGIES

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Testing children for allergies: why, how, who and when
An updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation


Keywords
allergy; asthma; atopic eczema/dermatitis; atopy; childhood; conjunctivitis; cough; drug allergy; food allergy; hymenoptera allergy; IgE tests; rhinitis; skin testing; urticaria

Abstract
Allergic diseases are common in childhood and can cause a significant morbidity and impaired quality-of-life of the children and their families. Adequate allergy testing is the prerequisite for optimal care, including allergen avoidance, pharmacotherapy and immunotherapy. Children with persisting or recurrent or severe symptoms suggestive for allergy should undergo an appropriate diagnostic work-up, irrespective of their age. Adequate allergy testing may also allow excluding a possible allergic trigger in common symptoms. We provide here evidence-based guidance on when and how to test for allergy in children based on common presenting symptoms suggestive of allergic diseases.
Table 2 Levels of evidences and grades of recommendation

<table>
<thead>
<tr>
<th>Level of evidences</th>
</tr>
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<tbody>
<tr>
<td>Level I Systematic reviews, meta-analyses, randomized controlled trials</td>
</tr>
<tr>
<td>Level II Two groups, non-randomized studies (e.g. cohort, case-control)</td>
</tr>
<tr>
<td>Level III One group, non-randomized (e.g. before and after, pre-test and post-test)</td>
</tr>
<tr>
<td>Level IV Descriptive studies that include analysis of outcomes (single-subject design, case series)</td>
</tr>
<tr>
<td>Level V Case reports and expert opinion that include narrative literature reviews and consensus statements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grades of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A Consistent level I studies</td>
</tr>
<tr>
<td>Grade B Consistent level II or III studies or extrapolations from level I studies</td>
</tr>
<tr>
<td>Grade C Level IV studies or extrapolations from level II or III studies</td>
</tr>
<tr>
<td>Grade D Level V evidence or troublingly inconsistent or inconclusive studies of any level</td>
</tr>
</tbody>
</table>

From www.cebm.net.
Total IgE- has no indication in diagnosing allergic diseases

But instead, total IgE plays role as:

• dosis-determining parameter in omalizumab therapy (B)

• Diagnostic parameter in allergic bronchopulmonary aspergillosis (B)

• algorhytm-parameter in risk calculation for provocation tests (B)
“Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests.”
IgE tests are necessary:

- To determine the necessity of allergen-free diet
  - E.g. if food allergies are suspected

- **Immunotherapy** - for clear diagnosis & follow up effectiveness

- Identification of high risk patients
  - E.g. hen’s in egg allergy there is a 20-25% sensibilisation to peanut - test (B)-should be offered..
Se sp IgE

• >0,1 ill. 0.35 kU/ml poz. Limit,
  • Different tests are not interchangable!

• **Good sensitivity** and NPV / true for SPT as well (C)

• **Lower specificity** (C)
  – Different PPV values for certain allergens.
    • Extracts are not standardized!
    • False positivities eg. Tree pollen/venom CH determinants

CRD-Component Resolved Dg

• **Recombinant allergens**
• Eg. Ara h 2 in peanut allergies – good PPV in children (C)
Prick test: Practical issues

- Trained staff!
- Interpretation: ≥ 3mm limit remained
  - In case of larger wheal reactions: the largest diameter is proposed to be measured
    » Constantinou (Papadopoulos), Int Arch Allerg Imm 2010
- Contraindications - remained:
  - Activ eczema, local steroid /immunmodulatory treatment antihistamines (≥3 days),
  - Disturbing effects of local steroids are questionable
- Wait min. 4-6 weeks after an acute allergic reaction (E)
- No age limit but careful interpretation below 2 years of age (C)
Provocations – mostly in food allergies

Gold standard : DBPCFC

Open provocations : acceptable in most cases (esp. in smaller babies)

If only subjective complaints : hide allergen (vehiculum)

Provocations: Not without risk!

( proper professional- technical background! ICU )
**Kruidoek voor dubbelblinde voedselprovocatie**

**Veilig en goed**

In wetenschappelijke kringen wordt steeds vaker gepleit voor Dubbelblinde Placebo-gecontroleerde Voedselprovocatiets tests als methode om een allergie voor bepaalde voedingsstoffen veilig en goed te testen. Een van de voordelen van deze manier van testen is dat er minder vaak sprake is van vals positieve uitslagen dan bij open tests.

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**Pastlaar antwoord**

Als pastlaar antwoord op deze ontwikkeling biedt Chef Martin nu een speciale kruidoek die kan worden ingezet bij het uitvoeren van dubbelblinde tests. De kruidoek wordt gemaakt op basis van gevaste recepten, ontwikkeld door Bij 'Vleugelenra' en al.

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**Vier varianten**

De speciale kruidoek is er in vier varianten, voor het testen van de volgende allergenen:

- Pinda
- Hazelnoot
- Kopytent
- Cashewnot

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**Onderscheidelijke kenmerken**

- Hoge einddoserings van het allergen.
- De kruidoek is direct na bereiding diegever en daardoor bij 18°C minimaal 6 maanden houdbaar.
- Bentig volgens HACCP-normen; positieve release (microbiologisch).
- De placebovariant van de kruidoek is door Chef Martin gecombineerd op identiteit met het betreffende allergen d.m.v. een snelle.
- De kruidoek is onder gecontroleerde omstandigheden bereid en zeer constant van samenstelling, waardoor een vast doseringschema kan worden gehanteerd.
- Door de producten tijdens het beproeven af te dekken, is de MilliTestreactie gemineraliseerd.
- Productspecificaties zijn beschikbaar.
- Productcodes maken verificatie van het type testvoeding achteraf altijd traceerbaar.
- Makkelijk te portieren.

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Dát is onze zorg voor leuk eten.
Likelihood ratios to diagnose allergy
EAACI FA & Anaphyl. Guidelines 2014

Figure I-C 1: Using likelihood ratios (LR) to diagnose allergy
Figure adapted from: Fagan T.J. (90)
The three arrows are examples of clinical situations described in the Table I-C below (Red arrow refers to scenario A, green to B and blue to C).

<table>
<thead>
<tr>
<th>Likelihood of clinical allergy from history</th>
<th>Low ($&lt;0.35$ or $&lt;3$)</th>
<th>Intermediate ($0.35$ to $&lt;15$ or $3$ to $&lt;8$)</th>
<th>High ($\geq 15$ or $\geq 8$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High e.g. Urticaria and wheeze on 2 exposures</td>
<td>Possible allergy</td>
<td>Probable allergy</td>
<td>Allergy</td>
</tr>
<tr>
<td>Intermediate e.g. Urticaria on a single exposure</td>
<td>Possible allergy</td>
<td>Possible allergy</td>
<td>Probable allergy</td>
</tr>
<tr>
<td>Low e.g. Non-IgE mediated symptoms</td>
<td>No allergy</td>
<td>Possible allergy</td>
<td>Possible allergy</td>
</tr>
</tbody>
</table>

Figure I-C 2: Using likelihood ratios (LR) to diagnose allergy
Children and adolescents in the possible allergy box require an OFC for a definitive diagnosis. Specific IgE and SPT values are specific for peanuts. Values associated with a high likelihood of clinical allergy are lower for egg, milk, and fish. Modified from Stiefel and Roberts (91).
Predictive values of algorithms in food challenge outcomes

PPV- s of clinical algorithms based on calculations using available parameters:

spIgE, total IgE, clinical signs/score, gender & age for risk predictions

Still in testing phase - may make provocation tests unnecessary...

(Dunn-Galvin, Hourihane, JACI 2011)
Unproven tests

IgG tests - not recommended for (IgE based) allergy diagnosis

IgG4:
role in tolerance? -
Immunotherapy- marker for follow up? 
(Sverremark-Ekström 2012)
Non validated tests – not recommended:

- Elektromagnetic conductance,
- kinesiology,
- hair analysis,
- iris-diagnostics,
- face-thermography,
- gastric fluid analysis
- Etc...- not recommended!
Molecular diagnostics (CRD) offers:

- Increasing diagnostic accuracy,
- Better evaluation for the efficacy of immunotherapies
- More effective prediction of cross-reactions.
- Less false diagnoses, less unnecessary diets
- Better quality of life
Molecular diagnostics (CRD)

Food allergens - risk of anaphylaxis/high vs. low

<table>
<thead>
<tr>
<th>Source</th>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Ara h 1, 2, 3, 9</td>
<td>Ara h 8, profilin, CCD</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a 8, 9, 14</td>
<td>Profilin, CCD</td>
</tr>
<tr>
<td>Walnut</td>
<td>Jug r 1, 2, 3</td>
<td>Profilin, CCD</td>
</tr>
<tr>
<td>Soy</td>
<td>Gly m 5, 6, (4)</td>
<td>Profilin, CCD</td>
</tr>
<tr>
<td>Rosacea fruits</td>
<td>Pru p 3, Mal d 3</td>
<td>Pru p 1, Mal d 1, profilin, CCD</td>
</tr>
<tr>
<td>Wheat</td>
<td>Tri a 14, Tri a 19</td>
<td>Profilin, CCD</td>
</tr>
</tbody>
</table>

KEY: CCD = Cross-reactive Carbohydrate Determinant
Test profile, birch allergy

Suggested birch pollen test profile

ImmunoCAP® ALLERGEN COMPONENTS

Birch

Bet v 1
Bet v 2
Bet v 4
Bet v 6

MAJOR BIRCH ALLERGEN
- PR-10 protein
- Specific for birch
- Cross-reactive
- Sensitive to heat and digestion
- Indication for birch pollen SIT

MINOR BIRCH POLLEN ALLERGENS

- Profilin
- Cross-reactive
- Rarely occurring as sole sensitizer in patients with clinical symptoms
- Sensitive to heat and digestion

- Polcalcin
- Cross-reactive
- Rarely occurring as sole sensitizer in patients with clinical symptoms

- Isoflavone reductase
- Cross-reactive
- Rarely occurring as sole sensitizer in patients with clinical symptoms

Sensitization to Bet v 2, Bet v 4 and/or Bet v 6 without Bet v 1 sensitization indicates low suitability for birch pollen SIT. Keep looking for the primary sensitizer.
CONSENSUS DOCUMENT

A WAO - ARIA - GA\(^2\)LEN consensus document on molecular-based allergy diagnostics

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Abstract

Molecular-based allergy (MA) diagnostics is an approach used to map the allergen sensitization of a patient at a molecular level, using purified natural or recombinant allergenic molecules (allergen components) instead of allergen extracts. Since its introduction, MA diagnostics has increasingly entered routine care, with currently more than 130 allergenic molecules commercially available for in vitro specific IgE (sIgE) testing.

MA diagnostics allows for an increased accuracy in allergy diagnosis and prognosis and plays an important role in three key aspects of allergy diagnosis: (1) resolving genuine versus cross-reactive sensitization in poly-sensitized patients, thereby improving the understanding of triggering allergens; (2) assessing, in selected cases, the risk of severe, systemic versus mild, local reactions in food allergy, thereby reducing unnecessary anxiety for the patient and the need for food challenge testing; and (3) identifying patients and triggering allergens for specific immunotherapy (SIT).

Singleplex and multiplex measurement platforms are available for MA diagnostics. The Immuno-Solid phase Allergen Chip (ISAC) is the most comprehensive platform currently available, which involves a biochip technology to measure sIgE antibodies against more than one hundred allergenic molecules in a single assay. As the field of MA diagnostics advances, future work needs to focus on large-scale, population-based studies involving practical applications, elucidation and expansion of additional allergenic molecules, and support for appropriate test interpretation. With the rapidly expanding evidence-base for MA diagnosis, there is a need for allergists to keep abreast of the latest information. The aim of this consensus document is to provide a practical guide for the indications, determination, and interpretation of MA diagnostics for clinicians trained in allergy.
Organ symptoms, related issues

*Atopic eczema* – if early onset and medium/strong signs

Higher risk for food allergies – to be excluded!

- $<3$ y, CM, hen’s egg allergens (B)
- $>3$ é: house dust mite! + local prevalent allergens (B)
Allergic urticaria, angioedema
Acute urticaria, angioedema

• Urtic: Starts within 2 hours, symptoms disappear within 24 hours
  – >24 hrs: **virus**, **drugs** (NSAID), histamin liberation, physical effect (eg. Cold, vasculitis: Schonlein-Henoch) more likely
  – HANO-, ACE inhibitors: angioedema without (!) urticaria
• IgE: based on history, targeted tests
• Panel –screens may increase false positivities – not recommended!
• Mostly: Cow milk, nuts, other food allergens, sometimes indoor allergens – or
• To rule out other triggers if necessary
Chr. urticaria

- Recurrent > 6 weeks lesion
- Rare in childhood,
- **Allergy test: extremely rarely diagnostic!**

- Background: parasites, chronic infection, autoimmunity, (coeliac disease too!) drug, mastocytosis, C1inh deficiency

- **Drug induced skin rashes:**
  - Diagnostics recommended in specialized centers for drug allergies: lactams, makrolides, sulfonamids, NSAID, anaesthesia-related drugs, latex, hypnotics, opioids, Anticonvulsives, contrast media
Anaphylaxis, childhood

Mostly food IgE

- During acute episodes: store serum (spec IgE, tryptase)

- **Tryptase**: Measurement within 1-3 hours (sometimes even normal)

- Later: Prick or Prick to Prick to be considered (more sensitive)

- **SpgE tests may be negative – if within 4-6 week anergic state - (E)**

- recombinant allergens may increase sensitivity.

- Provocation test: Only if there is no correlation btw. Signs and allergy tests
Gastrointestinal signs – role of history!

**IgE test** if other allergic sign/s is/are present - (even anaphylaxis)

Mostly non-IgE origin, if: vomiting, diarrhoea, reflux, colic, irritability, delayed growth

Chronic signs –extreme rare IgE type backgound ! –extensive diff dg, Consultation- GI specialist !

**Exclude**: FPIES, eosinophil GI diseases, - coeliakia

**coli**: Exclude fatigue, air-swallowing, reflux

- **If atopic signs present at a child** with excessive, inconsolable crying:
  - Exclude CMA & other food allergies

**Delay in growth**:

- Primary: Optimize food intake and follow up weight charts,
- Coeliakia, CF, immunodeficiencies –to be excluded
- (Rare: seroius atop. Dermatitis: oedema, hypalbuminaemia etc)

**Acute vomiting, diarrhoea**: think about infections, esp. in younger children!
Child with a sibling with food allergies

- Relatives: Higher risks –
- Child with a sibling with food allergies- when to test?
  - In case of moderate/ severe eczema
  - Symptomless sibling- testing depends on actual situation

Some other points:
- Extreme high sp IgE results- always check total IgE
  - maybe this is the reason
- IgE and activity of allergies: still to be discovered

Take home message:
Neither spIgE nor SPT can reflect the seriousness of the allergic reaction! It reflects the probability of an allergic reaction. (C)
Thank you for your attention!
Insect sting reactions

• Allergy diagnostics: only if the sting resulted in a systemic reaction!

• Local reactions do not indicate allergy testing! (B)

• Allergy testing may establish
  – Immunotherapy / prevention

• Additional tests if necessary: basophil activation, recombinant allergens, basal se tryptase (to rule out mastocytosis)
Respiratory symptoms I.

- **Rhinitis**: asthma should be ruled out always!
- **Caugh, IgE tests if:**
  - Persistent (weeks or more),
  - Recurrent (>2/year)
  - Dry / nocturnal
  - Induced
  - + if allergy-risk is higher (e.g. familial or individual)
  - If asthma medication can help …

- In other cases it is primary to rule out other possible causes
<table>
<thead>
<tr>
<th>Table 6 Potentially serious disorders that are associated with chronic coughing in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cystic fibrosis</td>
</tr>
<tr>
<td>• Immunodeficiency</td>
</tr>
<tr>
<td>• Primary ciliary disorders</td>
</tr>
<tr>
<td>• Persistent bacterial bronchitis</td>
</tr>
<tr>
<td>• Bronchiectasis</td>
</tr>
<tr>
<td>• Recurrent aspiration, gastro-oesophageal reflux, laryngeal cleft, H-type tracheoesophageal fistula, swallowing incoordination with or without neurodevelopmental or neuromuscular disorder</td>
</tr>
<tr>
<td>• Retained inhaled foreign body</td>
</tr>
<tr>
<td>• Tuberculosis</td>
</tr>
<tr>
<td>• Anatomical abnormality, tracheomalacia, bronchomalacia, congenital lung malformation</td>
</tr>
<tr>
<td>• Interstitial lung disease or obliterative bronchiolitis</td>
</tr>
<tr>
<td>• Cardiac disease</td>
</tr>
</tbody>
</table>
Chronic/recurrent wheeze

All children with
• Chronic or recurrent (>3 times) wheeze, not triggered by upper airway infections,
• or possible asthma diagnosis
should be tested for IgE sensitizations [A].

Need for test is increasing by:
  Increasing age, positive family history, the presence of additional allergic symptoms.
Bee/wasps- Venom diagnostics

Complete extracts and recombinant components are both needed for precise patient assessment.

ImmunoCAP® COMPLETE EXTRACTS
- i1 (Honey bee), i3 (Common Wasp), i77 (Paper Wasp)

ImmunoCAP® COMPONENTS
- rApi m 1 (i208), rVes v 1 (i211), rVes v 5 (i209), rPol d 5 (i210)

SIT CANDIDATE
- Honey bee
- Honey bee + Common/Paper Wasp
- Common/Paper Wasp

RECOMMENDED TESTS:
- ImmunoCAP Tryptase
  Measure tryptase baseline levels before SIT to assess risk for severe reactions
- MUXF3 CCD o214 (from Bromelain)
  - Pure CCD containing only the MUXF3 carbohydrate epitope
  - Cross-reactivity marker for CCDs

*rPol d 5: Common especially in the Mediterranean areas.
Suggested profiles for SIT decision

### Phleum pratense

- Specific components for grass
- Indication for grass pollen SIT

### Phl p 1, Phl p 5

- Specific components for grass

### Phl p 2, Phl p 4, Phl p 6, Phl p 11

- Cross-reactive allergen components
- Often minor allergens which may not be available in sufficient amount in the SIT extract
- IgE to Phl p 7 and 12 alone indicate low suitability for grass pollen SIT. Keep on looking for the real cause.

### Phl p 7, Phl p 12

- Specific components for grass
- Data on SIT outcome are not available in literature

Timothy components are suitable markers for many grass due to high degree of similarity between species.

- **ARUNDINO IDEAE**
  - Phragmites (Common reed)

- **CHLORIDO IDEAE**
  - Cyperus (Cyperus grass)

- **PANICO IDEAE**
  - Zoysia (Zoysia grass)
  - Sorghum (Johnson grass)

- **POACEAE** (Gramineae)
  - Elymus (Wild rye grass)
  - Triticum (Cultivated wheat)
  - Hordeum (Barley)
  - Holcus (Velvet grass)
  - Anthoxanthum (False oat-grass)

- **POOIDEAE**
  - Phleum (Timothy)
  - Alopecurus (Meadow foxtail)
  - Agrostis (Redtop)
  - Dactylis (Salt grass)
  - Lolium (Rye grass)
  - Dactylis (Cocksfoot)
  - Poa (Meadow grass)
  - Festuca (Meadow fescue)

- **Secale (Cultivated rye)**

- **Bromus (Brome grass)**

Grasses and their botanical relations, adapted from L. Ymam (2014)