

WISC 2014

Symposium: Asthma and Allergy in Children

Monday, December 8, 2014: 01:00 PM - 02:30 PM, Sul America, Sala B1

Challenges in Diagnosing Allergic Triggers in Childhood Asthma

Elham Hossny, MD, PhD

Objectives

To know the challenges in diagnosing asthma triggers:

- Allergen specific IgE testing
- Component testing
- Allergen challenge tests

Allergens in childhood asthma:

- Indoor: e.g. dust mite, animal dander, molds, mice, and cockroach
- Outdoor: e.g. pollens, molds
- Food allergens: do not typically cause chronic respiratory disease

The indoor allergen profile differs in various geographic areas and urban communities. Local allergens are sometimes not identified in many developing countries. Some important allergens such as *Blomia tropicalis* should be included in the skin test battery of tropical countries.^{1,2}

Interpretation of tests requires consideration of environmental exposures (housing, pets, and geographic floristic patterns), medical history (nature of symptoms, timing in relation to exposures) and disease characteristics (e.g. pollen allergy is uncommon in infancy).³

Tests for specific IgE may be influenced by cross-reactive proteins that may or may not have clinical relevance to disease.³ The cockroach allergen tropomyosin has potential cross reactivity with mite and shrimp allergens.⁴ Allergic sensitization to more than one mammalian animal is common, which might reflect co-sensitization or cross-reactivity. In some countries sensitization to furry animals is associated with more severe allergic disease.⁵

Screening panels of food allergens in asthma without previous consideration of the history is not recommended, because sensitization without clinical allergy is common. For example, ~8% has positive test results for peanut, but ~1% is clinically allergic.³ Food allergy in patients with asthma seems to be more common in infants and young children.⁶

Testing for latex allergy is primarily indicated in risk groups, i.e. spina bifida, urogenital malformations, frequent operations, and early exposure to latex. The symptoms are like other IgE-mediated allergies. Cross-reactions to banana, avocado, kiwi, chestnut, papaya,

and figs are reported. Even cross-reactions to potato and tomato have been reported as well to *Ficus benjamina*.^{7,8}

The essential components of allergy diagnosis⁹

- 1st line approach: clinical history
- 2nd line approach: allergen extract-based IgE tests (in vitro specific IgE or skin prick test) as a second-line investigation
- 3rd line approach: molecular-based allergy (MA) diagnostics for patients in whom first- and second-line investigations were inconclusive

Provocation testing e.g. oral, nasal, bronchial Challenge is occasionally needed

To screen for allergy in a wheezy infant, select a small panel of common triggers. A multi-allergen test that contains several common perennial allergens in one test (e.g. dust mite, dog dander, and mold) may be used. A positive test can, at less cost, identify a child whose symptoms may relate to exposure to a specific allergen and warrant further specific testing or referral.³

Skin prick testing in childhood asthma¹⁰

Diagnostic analysis of skin prick tests or specific IgE in serum is of no value if it is interpreted without reference to medical history.

Common errors in SPT

- Tests too close together (< 2 cm)
- Induction of bleeding, leading possibly to false-positive results
- Insufficient penetration of skin by lancet leading to false-negative
- Spreading of allergen solutions during the tests.

Causes of false positive results

- Dermatographism
- Irritant reactions
- Non-specific enhancement from a nearby strong reaction

Causes of false negative results

- Extracts of poor initial potency or subsequent loss of potency.
- Drugs modulating the allergic reaction.
- Diseases attenuating the skin response.
- Improper technique (no or weak puncture).
- Limited local production of allergen-specific IgE.

Effect of Medications on SPT results

- Most antihistamines and anti-depressants suppress skin tests for 3-7 days.
- H2 antagonists have no, or a very minor, effect.
- Bronchodilators do not affect skin tests.

- Short-term and low dose oral corticosteroids have no effect. Reports vary on long-term high-dose use.

Predictive value of SPT

A negative skin prick test may exclude an IgE-mediated reaction (good negative test) but many patients with a positive test do not react upon food ingestion. The positive predictive value is $\leq 50\%$ and negative predictive value $\geq 95\%$

Repeated testing may only be needed, mainly to detect new sensitizations in children and when changes in symptoms have occurred. Prick testing can only be performed on healthy skin. Patients with widespread urticaria or eczema (e.g. atopic dermatitis) cannot be tested in areas of affected skin. Neurological disorders as well as infectious disease (e.g. leprosy) can lead to false-negative SPTs.¹⁰

Skin test reactivity decreases with allergen-specific immunotherapy to inhalant allergens, but skin tests cannot be used to assess the efficacy of immunotherapy in practice. Moreover, skin tests cannot be used to decide on the cessation of immunotherapy.^{11,12}

Serum allergen specific-IgE testing

It is recommended when SPT cannot be done:

- Patient cannot stop anti-histamines
- Immediately (up to 4-6 weeks) following an anaphylactic event or risk of anaphylaxis
- Patient is morbidly afraid of skin testing
- Severe eczema with no site for testing
- Dermatographism

False positive a false negative results

False-positive results of blood testing can occur due to nonspecific binding of antibody in the assay. False-negative results occur in patients who have true IgE mediated disease as confirmed by skin testing or allergen challenge. The sensitivity of blood allergy testing is approximately 25% to 30% lower than that of skin testing, based on comparative studies.^{13,14}

Limitations of blood testing of specific IgE

Levels of specific IgE may depend on age, allergen specificity, total serum IgE, and, with inhalant allergens, the season of the year. Levels measured by different commercial assays are not always equivalent, so a clinician should select the same immunoassay if possible when assessing a patient over time. Another limitations are the cost and delay in obtaining the results.^{14,15}

Component resolved diagnosis (CRD)

Component-resolved diagnostics (CRD) utilize purified native or recombinant allergens to detect IgE sensitivity to individual allergen molecules and have become of growing importance in clinical investigation of IgE-mediated allergies.¹⁶ It is now time for the

clinician to integrate this knowledge and use it when needed to improve the accuracy of diagnosis and thus provide more precise therapeutic and avoidance measures.¹⁷

The molecular structures of many allergens have been characterized and are commercially available as recombinant products; however, guidelines or consensus on their use have not been defined. There is evidence that more than 95% of patients with IgE antibodies to Ara h 2 in combination with Ara h 1 or Ara h 3 have clinical peanut allergy. Component resolved diagnosis has a place in the investigation of children with insect allergy. Assessment of IgE to Api m 1 and Ves v 5 is helpful for the decision of whether immunotherapy to bee and wasp allergens respectively should be recommended or not. Component resolved diagnosis may also be helpful in anaphylactic reactions in patients with suspected wheat or soy allergy.¹⁸

*Molecular-based allergy (MA) diagnostics may play an important role in three key aspects of allergy diagnosis:*¹⁸

- Resolving genuine versus cross-reactive sensitization in poly-sensitized patients
- Assessing the risk of severe systemic versus mild reactions in food allergy, thereby reducing the unnecessary need for food challenge testing
- Identifying patients and triggering allergens for specific immunotherapy

In-Vivo Provocation Tests

Challenge of the affected organ by serial dilutions of the suspected allergen source material, e.g. food or drug. It can result in dangerous clinical reactions and should only be performed by experienced persons with access to life saving equipment.

Bronchial provocation testing (BPT):

It can confirm environmental allergy but are not often undertaken for clinical purposes. It is not needed in case of full agreement between the history and specific IgE tests but may be performed in equivocal cases with continuous symptoms. It should not be performed until the age of 5 - 6 years.^{3,7}

*Contraindications of BPT:*¹⁹

- Diseases of the immune system, or other relevant organic disease
- Conditions that make it difficult to manage adverse reactions, such as coronary artery or patients on beta adrenergic blockers
- Patients who developed severe or generalized reactions during previous BPT

When to do a food challenge?

- When the SPT result is positive but not conclusive e.g. > 3 mm but less than 8 mm
- When the Specific IgE level is positive but not high enough to diagnose allergy
- When mother insists that her child reacts to a food although the test results are negative
- In cell-mediated reactions after successful elimination

When not to do food challenge?

- Recent severe systemic reaction or anaphylaxis
- When positive test results makes challenge unnecessary (e.g. Children with convincing history to egg and positive SPT ≥ 8 mm and/or specific IgE (CAP) ≥ 17.5 Ku/L to egg.

*Do not use the following tests*³

- Lymphocyte stimulation
- Facial thermography
- Gastric juice analysis
- Hair analysis
- Applied kinesiology
- Provocation-neutralization
- Allergen-specific IgG/IgG4
- Cytotoxic assay
- Electrodermal test (VEGA)
- Mediator release assay

Key Notes

- History is the most important tool in allergy diagnosis
- A positive test of sensitization does not necessarily mean that the person will react on exposure
- Be aware of the levels of positivity that have a high positive predictive value for an allergen
- The value of serum total IgE in the diagnosis of allergy is limited

Unmet Challenges

Allergy diagnosis is facing more basic challenges in many parts of the world:

- Pollen counts not determined
- Indoor allergen loads are unknown
- Little knowledge about relevant allergens

REFERENCES

1. Fernandez-Caldas E, Puerta L, Mercado D, Lockey RF, Caraballo LR. Mite fauna, Der p I, Der f I and Blomia tropicalis allergen levels in a tropical environment. Clin Exp Allergy 1993;23:292-7.
2. Ahluwalia SK, Peng RD, Breyse PN, Diette GB, Curtin-Brosnan J, Aloe C, Matsui EC. J Allergy Clin Immunol 2013;132(4):830-5.
3. Sicherer SH, Wood RA; American Academy of Pediatrics Section On Allergy And Immunology. Allergy testing in childhood: using allergen-specific IgE tests. Pediatrics 2012;129:193-7.

4. Santos AB, Chapman MD, Aalberse RC, Vailes LD, Ferriani VP, Oliver C, Rizzo MC, Naspitz CK, Arruda LK. Cockroach allergens and asthma in Brazil: identification of tropomyosin as a major allergen with potential cross-reactivity with mite and shrimp allergens. *J Allergy Clin Immunol* 1999;104(2 Pt 1):329-37.
5. Konradsen JR, Fujisawa T, van Hage M, Hedlin G, Hilger C, Kleine-Tebbe J, Matsui EC, Roberts G, Rönmark E, Platts-Mills T. Allergy to furry animals: New insights, diagnostic approaches, and challenges. *J Allergy Clin Immunol* 2014 Oct 1. pii: S0091-6749(14)01199-3. doi: 10.1016/j.jaci.2014.08.026. [Epub ahead of print]
6. El-Gamal YM, Hossny EM. Respiratory food allergy. *Pediatr Ann* 2006;35(10):733-40.
7. Brehler R, Kutting B. Natural rubber latex allergy: a problem of interdisciplinary concern in medicine. *Arch Intern Med* 2001;161(8):1057-64.
8. Høst A, Andrae S, Charkin S, Diaz-Vázquez C, Dreborg S, Eigenmann PA, Friedrichs F, Grinstead P, Lack G, Meylan G, Miglioranza P, Muraro A, Nieto A, Niggemann B, Pascual C, Pouech MG, Rancé F, Rietschel E, Wickman M. Allergy testing in children: why, who, when and how? *Allergy* 2003;58(7):559-69.
9. Canonica GW, Ansotegui IJ, Pawankar R, Schmid-Grendelmeier P, van Hage M, Baena-Cagnani CE, Melioli G, Nunes C, Passalacqua G, Rosenwasser L, Sampson H, Sastre J, Bousquet J, Zuberbier T; WAO-ARIA-GA2LEN Task Force: Allen K, Asero R, Bohle B, Cox L, de Blay F, Ebisawa M, Maximiliano-Gomez R, Gonzalez-Diaz S, Haahtela T, Holgate S, Jakob T, Larche M, Matricardi PM, Oppenheimer J, Poulsen LK, Renz HE, Rosario N, Rothenberg M, Sanchez-Borges M, Scala E, Valenta R. A WAO - ARIA - GA2LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J* 2013, 6(1):17.
10. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, Canonica GW, Carlsen KH, Cox L, Haahtela T, Lodrup Carlsen KC, Price D, Samolinski B, Simons FE, Wickman M, Annesi-Maesano I, Baena-Cagnani CE, Bergmann KC, Bindeslev-Jensen C, Casale TB, Chiriac A, Cruz AA, Dubakiene R, Durham SR, Fokkens WJ, Gerth-van-Wijk R, Kalayci O, Kowalski ML, Mari A, Mullol J, Nazamova-Baranova L, O'Hehir RE, Ohta K, Panzner P, Passalacqua G, Ring J, Rogala B, Romano A, Ryan D, Schmid-Grendelmeier P, Todo-Bom A, Valenta R, Woehrl S, Yusuf OM, Zuberbier T, Demoly P; Global Allergy and Asthma European Network; Allergic Rhinitis and its Impact on Asthma. Practical guide to skin prick tests in allergy to aeroallergens. *Allergy* 2012;67(1):18-24.
11. Bousquet J, Maasch HJ, Hejjaoui A, Skassa-Brociek W, Wahl R, Dhivert H, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. III. Efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. *J Allergy Clin Immunol* 1989; 84(4 Pt 1):546-56.
12. Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Walter Canonica G, Merk H, Worm M, Wahn U, Bousquet J. GA² LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010;65(12):1525-30.

13. Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, Sicherer S, Golden DB, Khan DA, Nicklas RA, Portnoy JM, Blessing-Moore J, Cox L, Lang DM, Oppenheimer J, Randolph CC, Schuller DE, Tilles SA, Wallace DV, Levetin E, Weber R; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol* 2008; 100(3 Suppl 3):S1-148.
14. Siles RI, Hsieh FH. Allergy blood testing: A practical guide for clinicians. *Cleve Clin J Med* 2011;78(9):585-92.
15. Hamilton RG, Williams PB; Specific IgE Testing Task Force of the American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma and Immunology. Human IgE antibody serology: a primer for the practicing North American allergist/immunologist. *J Allergy Clin Immunol* 2010;126(1):33-8.
16. Treudler R, Simon JC. Overview of component resolved diagnostics. *Curr Allergy Asthma Rep* 2013;13(1):110-7.
17. Luengo O, Cardona V. Component resolved diagnosis: when should it be used? *Clin Transl Allergy* 2014;4:28.
18. Wolthers OD. Component-resolved diagnosis in pediatrics. *ISRN Pediatr* 2012;2012:806920.
19. Melillo G, Melillo G, Bonini S, Cocco G, Davies RJ, de Monchy JG, Frølund L, Pelikan Z. EAACI provocation tests with allergens. Report prepared by the European Academy of Allergology and Clinical Immunology Subcommittee on provocation tests with allergens. *Allergy* 1997;52(35 Suppl):1-35.