

Allergy Testing

Competency:

The resident should be able to:

1. Understand how skin testing and RAST are done.
2. Know when and who should be referred to an allergist.
3. Understand in general how these tests are interpreted.
4. Recognize that RAST testing should never be interpreted outside of the clinical context and used to unnecessarily restrict foods.

Case:

J.R. is a 4 year old girl seen in your clinic for URI-like symptoms for two years. Her mom complains that she sneezes frequently and seems to have constant year round rhinorrhea and congestion. Her last pediatrician has tried flonase, singulair and loratadine, none of which provided much relief, although they have not been used consistently. For the last year, she has also developed a cough which now she has every night. She does not have a history of food allergies but did have eczema as a young infant which mom controlled with a topical hydrocortisone ointment. She has a brother with asthma. She lives with her mother, father and brother. They have carpet throughout the house and a dog which has full range of the home. Mom wants to know if the dog could be contributing to these problems and would also like for you to provide her daughter with some relief. What do you do? What do you tell mom?

References:

1. Sampson, H, Albergo R. Comparison of results of skin tests, RAST and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 74:26, 1984; 26-33.
2. Cartwright, R., Dolen, W. Who Needs Allergy Testing and How to Get it Done. *Pediatrics in Review*; April 2006, Vol 27(4). 140-145.
3. Chinoy B, Yee E, Bahna S. Skin testing versus radioallergosorbent testing for indoor allergens. *Clinical and Molecular Allergy*; April 2005, Vol 3:4.
4. Hamilton, R, Adkinson Jr N. Assessment and Modulation of the Immune Response. *J Allergy Clin Immunol* 111:2, 2003.

What is allergy testing?

Allergy testing encompasses a variety of assays used to aid in both the diagnosis and management of a variety of atopic diseases including allergic rhinitis, asthma, eczema and food allergies. Two of these methods will be discussed in this paper, skin testing and in vitro IgE immunoassays, the latter more commonly known as RAST (radioallergoimmunosorbent assay).

Skin testing uses antigens to directly challenge mast cells present in the skin whereas RAST testing measures the quantity of allergen specific IgE in the blood. In the proper clinical setting, these tests can be used to detect if a patient is sensitized to various allergens which can trigger IgE mediated allergic disease.

What is skin testing?

Purified antigen is introduced into the skin. The skin reaction to the antigen is then measured. There are various ways to perform skin testing including skin test puncture method, prick skin testing, and intradermal testing. The antigens most commonly tested are environmental and food derived allergens.

1. Skin test puncture method.

The most common type is the skin test puncture method. A plastic disposable device with 8 arms with 2mm prongs on each arm is dipped in antigenic extract and used to superficially puncture the skin using a twisting or rocking motion. The allergen alternatively can first be placed on the skin. Then excess reagent is removed with gauze or tissue paper and the immediate wheal and erythema is read at 15 to 20 minutes, the time at which it reaches its maximum diameter. A positive control, usually histamine is also placed to make certain no anti-histamines have been taken which can interfere with the testing results. A negative control, glycerinated saline (which is the solvent used to dissolve the antigen) or normal saline is also placed to make certain the patient is not dermatographic and falsely being identified as sensitive to all tested allergens.

Interpretations of the wheal and flare can vary but most agree that a positive test is 3mm or larger than negative control. Commonly the proximal forearm or back is tested, and if 2 devices are used, up to 16 allergens can be tested at one time.

2. ID testing.

Intradermal skin testing is another form of skin allergy testing. It involves using a 26 or 27 gauge syringe to introduce an allergen into the dermal layer of the upper arm or forearm with 0.02ml injected to produce a 2-3 mm superficial bleb.

Comparing and contrasting ID testing and skin test puncture method.

Both of these tests involve detecting the presence of allergen specific IgE bound to mast cells in the skin. Comparing the puncture method to ID testing, the skin test puncture

method has clear advantages. It is quick and can test multiple allergens at the same time. Skin prick testing can be done with food derivatives which is not done with ID testing. Prick testing is simpler, because it doesn't involve needles, is less expensive and importantly, it is safer. ID testing carries an increased risk of anaphylaxis which can be fatal. However ID testing is still preferred in certain situations such as for low potency extracts such as antibiotics, anesthetics and insect venoms. ID testing is 500-1000 times more sensitive than prick testing therefore a much smaller concentration of antigen is used. ID testing can also be done when an aeroallergen shows a negative skin prick test but there is still a high suspicion of allergy. This increased sensitivity however also means that introducing too large a bleb or injecting too deeply produces false positives.

Factors that affect skin testing results:

Patient Factors:

1. Patients taking antihistamines

In skin testing the wheal and flare is largely due to the release of histamine from mast cells so antihistamines will blunt this response. Oral and topical H1 and H2 antagonists such as eye drops, nasal sprays, TCAs, tranquilizers and anti-emetics all inhibit testing and it is best to stop them before testing. First generation sedating antihistamines such as diphenhydramine or hydroxyzine should be stopped for 72 hours prior to testing while long acting nonsedating drugs such as desloratidine, cetirizine or fexofenadine should be stopped for a week before testing.

2. Patients with extensive atopic dermatitis

Even in unaffected skin these patients may still have decreased responsiveness.

3. Patients with dermatographism

These patients will obviously have false positives.

4. Patients with recent history of anaphylaxis

Theoretically these patients are depleted of neurogenic mediators and a false negative could ensue, thus testing should be deferred for a week after the event.

5. Steroid use greater than one week

Short term topical or oral steroid use will not affect results but use for greater than a week could inhibit mast cell degranulation resulting in a false negative test.

6. Age

Infants less than 2 years old may have false negative skin prick tests even if they do have true IgE mediated food allergy because of decreased skin reactivity.

7. Chronic Disease

There is also literature suggesting decreased responsiveness in pts with chronic renal failure, cancer patients, and those with CNS injuries.

8. The quality of the antigen.

At present, all allergen extracts used clinically are from natural sources, thus they vary in protein composition, allergenic potency and immunoreactivity not just from manufacturer to manufacturer but also from batch to batch. One generic rule of allergy diagnostics is that each allergen reagent will detect a slightly different population of IgE antibodies and thus the test results should not be viewed as interchangeable between manufacturers of skin testing reagents and/or serum based IgE antibody assays. Because of this variability, a negative test in an otherwise convincing history should be repeated using fresh foods rather than commercially prepared extracts.

9. Timing.

Test results can differ depending on when they are performed. For example, testing a patient for allergy to outside allergens during pollen season would produce a stronger reaction than any other time of the year.

10. Experience.

There are numerous tests commercially available and vary in performance characteristics. Therefore it takes qualified and trained personnel in order for the test results to be reproducible and reliable.

What is RAST?

RAST was the first clinical assay reported for the detection of allergen specific IgE antibodies in human serum. A specific allergen is bound to a paper disk. Human serum is added resulting in antibodies binding to the allergen. Bound IgE is then tagged with a radiolabeled IgG and the radioactivity is then measured using a gamma counter. The result is proportional to the amount of free allergen specific IgE in the test serum. These tests are generally considered second choice by most allergists because they are less sensitive compared to skin testing and are more of an indirect measure of IgE rather than directly measuring histamine release by caused by IgE receptor signaling on mast cells. In the past, most allergists would use RAST testing only in situations where skin testing would be considered unreliable or unsafe.

Newer second generation IgE antibody assays have now evolved which are more sensitive and specific than their older first generation counterparts. This newer test is called the ImmunoCAP allergen specific IgE assay, more commonly known as CAP-RAST, and has been demonstrated to be a more accurate quantitative measure of allergen specific serum IgE by using better quality allergen extracts, uses better binding materials and better detection methods. In addition, it does not rely on radioisotopes to detect IgE. This test has largely replaced RAST and is fairly equal to skin testing in terms of sensitivity and specificity.

Who do you refer to an allergist? (Adapted from Consultation and referral Guideline developed by AAAAI):

- All patients who have had an anaphylactic event

- Patients with suspected or proven asthma or CF who have pulmonary infiltrates and peripheral blood eosinophilia (to diagnose allergic bronchopulmonary aspergillosis)
- Severe persistent asthmatics
- Asthmatics who have seasonal symptoms or suspicion of inhalant triggers (all asthmatics with allergies should be referred to an allergist)
- Patients with prolonged or recurrent allergic conjunctivitis
- All patients with moderate to severe atopic dermatitis (35% of these children have food allergies)
- All patients with a history of adverse reaction to a drug and might require it in the future (NSAIDs, penicillin, local anesthetics, bactrim for HIV patients)
- All patients with suspicion of food allergy secondary to symptoms including itchy mouth, urticaria, or GI symptoms
- All patients who report adverse reactions to food additives such as MSG (very few food additive allergies are validated after evaluation)
- All patients who are avoiding foods because of the suspicion of allergy (only one third of perceived adverse reactions to food are verified after allergy testing)
- Infants with recalcitrant GE reflux, and older children with reflux and dysphagia.

How do you interpret the results?

Possibly the single most important fact about allergy testing is that the results should never be interpreted outside of the clinical context. A positive skin test and positive RAST alone is not sufficient to diagnose allergy without a good history and physical exam. If the results do not agree with the clinical picture, retesting is always indicated. Many times patients are unnecessarily restricted from eating foods based solely on RAST testing which could affect that patients overall growth and development. Therefore proper interpretation of test results is essential in the safety and overall health of the patient.

In general, for food, the positive predictive accuracy of prick skin tests are less than 50% compared to the gold standard which is double-blind, placebo-controlled food challenge (DBPCFC). Therefore a positive skin test can suggest an allergy and warrants confirmation with a DBPCFC. However a negative skin test virtually excludes IgE mediated reactions, with a negative predictive accuracy >95%. The exception to this is in the case of a good history of a systemic anaphylactic response to a food. A positive prick skin test in face of a previous anaphylactic response can be considered diagnostic because of the danger of doing a DBPCFC (Sampson, JACI 1999). CAP-RAST, unlike standard RAST, has been shown in some studies to have a positive predictive accuracy comparable to prick skin testing for egg, milk, peanut and fish.

Conclusion:

In conclusion, allergy testing can serve as a valuable tool in the management of IgE mediated allergic disease. When interpreted within the clinical context and not in isolation, allergy testing can help elucidate a culprit in allergic disease which warrants further testing, or simply rule out an allergen that could possibly have been unnecessarily restricted.

References:

1. Sampson, H, Albergo R. Comparison of results of skin tests, RAST and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 74:26, 1984; 26-33.
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