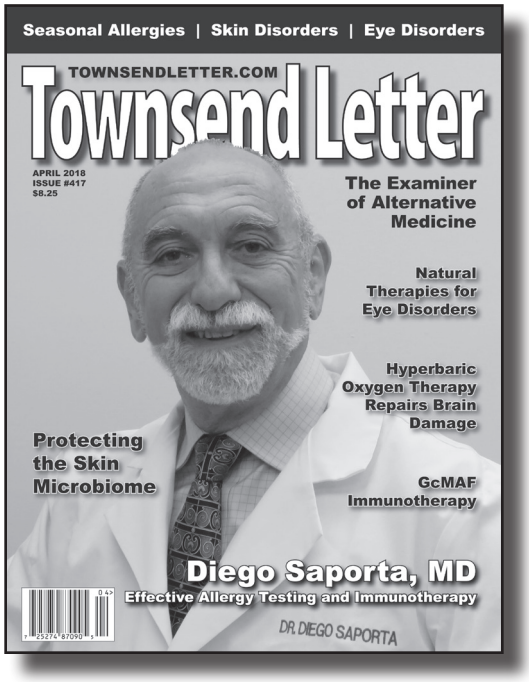


## *On the cover*

# Management of the Allergic Patient: The Role of Different Diagnostic Tests

**by Diego Saporta, MD, and David Hurst, MD, PhD**

**Introduction**

Management of the allergic patient is based on diagnosing which allergens trigger the symptoms and then mixing a vaccine that will be administered for several years. This treatment is known as immunotherapy.

Every allergist has encountered patients whose clinical presentation is that of allergy, but the testing is negative. Yet those same patients respond to nasal steroids and antihistamines. This quandary suggests that either the diagnosis or the test is wrong and has led to much discussion among clinicians.[1]

Most in-vivo allergy testing for in the USA and Europe relies on the skin prick test (SPT)[2] despite its sensitivity of 50-90%.[3] Prick testing is recognized to be extremely specific, which makes it ideal in selecting patients for scientific studies. This is accomplished by sacrificing sensitivity. The negative predictive value of a negative SPT for cat allergen is 72%.[4] The positive predictive value for *Dermatophagoides pteronyssinus* ranges from 29% to 43%.[5]

There are two schools of thought in reference to the management of the allergic patient. The most popular is that based on the work of Noon[6] in the 1900s and adopted as described in the guidelines of both the American Academy of Allergy Asthma & Immunology (AAAAI) and the European Academy of Allergy and Immunology (EAACI). The less popularized method is that derived from the work of Hansel and Rinkel[7,8] in the 1940s and adopted by a group of allergy practitioners that use these concepts according to the guidelines of the American Academy of Otolaryngic Allergy (AAOA),[9] Pan American Allergy Society (PAAS) [10] and American Academy of Environmental Medicine(AAEM).[11]

Despite huge advances in molecular biology, recognition and typification of allergens, and the ability to produce allergenic molecules that are safer to inject,[12] no major changes in skin testing techniques have occurred since this type of treatment was described in the 1930s -1940s.[13]

There are differences between these two schools in reference to the management of the allergic patient. These differences have existed for many decades. Most of the disagreement revolves around the definition of what constitutes an allergic reaction and what test is used for the diagnosis of significant allergens.

Understanding these differences becomes important when deciding which method to use when testing and treating a patient, as the management of these patients can potentially be different as will be explained in this paper.

The allergic patient has a dysfunctional immunological system, with a predominance of the Th2 response to allergens such as dust or animal dander. With Specific Immunotherapy (SIT), the Th2-dominant immune response involving IgE, IL-5, eosinophil, and mast cell production is modified towards a Th1 response,[14] leading to a decline in allergen-specific IgE, an increase in allergen-specific IgG and production of anti-inflammatory cytokines IL10 and IL12 [15,16]

SIT vaccines contain the allergens actually responsible for the symptoms that the patient develops. Vaccines can be given through injections ("allergy shots") or sublingual drops. Small amounts of the appropriate allergens are administered at small intervals with increasing doses over a long period of time. This leads to gradual desensitization to those offending allergens. Obviously, if the responsible allergens cannot be identified or are only partially identified, the results of the treatment will not be as successful.

Clinically important is the difference between the concept of the few "predominant" or "relevant allergens" versus the concept of the "total allergic load".

**Relevant Allergens vs Total Allergic Load**

The AAAAI and EAACI follow the concept of the "relevant allergen(s)" [17-19] The objective of the test is to diagnose only those allergens that are considered the most important for a geographical area or for a particular patient. According to this concept, using only this minimal number of allergens is sufficient to treat the patient, with the idea that these few allergens are responsible for the majority of the symptoms the patient has developed and therefore a vaccine containing only these allergen(s) will be sufficient to produce symptom-control.[17,20]

Practitioners from AAOA, PAAS and AAEM use the concept of the "total load."[21,22] The idea is that the patient is confronted with a multitude of aggressions (not only allergenic) that eventually lead to development of the symptoms. Decreasing the reactivity to as many of these environmental offenders as possible, the better the symptoms can be eliminated. Limiting the discussion only to the field of allergies, the "total load" concept dictates that the more allergens that can be desensitized, the better the long-term results of the treatment. Thus, the idea of treating any allergen that is positive by an allergy test becomes important.

Comparing the different tests used for the diagnosis of allergic conditions shows that there are significant differences in their potential for demonstrating reactive allergens.

**Different Types of Tests**

Allergy tests can be done "in-vitro" or "in-vivo." In-vitro tests are run on a sample of the patient's blood. Usually known as "RAST tests," they evaluate the presence of antibodies against different allergens. Technically, RAST refers to the original test that relied on radioactive technology which is no longer used. Current in-vitro tests use ELISA or Immuno-cap technology. Since the modern definition of allergy states that it is an IgE-mediated phenomenon, only in-vitro tests that measure IgE antibodies against the tested allergens are usually used. It is not infrequent for the usual battery of "RAST tests" to yield a negative result that contradicts a convincing patient history. This circumstance can be explained if the four types of hypersensitivity reactions described by Gell and Coombs are considered.[23] Classic IgE-mediated allergy is a Type 1 Gell and Coombs reaction, but the other three classes are triggered by other mechanisms that are not detected by an artificial mechanical test. This shortcoming is addressed by skin testing.

**In-Vivo Tests**

The most commonly used in-vivo tests are the SPT and the intradermal (ID) test. In the SPT, the allergen is deposited on the surface of the skin. Even though the prick device is pressed against the skin, the integrity of the skin is not violated, therefore the allergen will not penetrate the dermis. In the ID test, the allergen is directly introduced into the dermis by injection.

The allergy guidelines attribute to the SPT a high level of usefulness.[24] It is considered highly specific. Patients treated by most general allergists are usually managed based on the information obtained from SPT's, commonly performed with a multi-prick device so several allergens are tested at the same time. It would appear from the information in the guidelines[24] and other literature that the SPT is the "gold standard" considered as the "core diagnostic test for type I immediate allergy."[25]

**SPT vs ID Test**

A skin test being reactive (positive) is dependent on the mast cell degranulating and producing IgE, histamine, and other bio-active chemicals when challenged with an allergen to which the patient's mast cells have been sensitized.

Because the mast cells populate the dermis usually close to the blood vessels,[26] it is only logical to assume that the diagnostic power of a test that deposits the allergen literally in the vicinity of the mast cells (ID test) will have better diagnostic power than a test that deposits the allergen in the surface of the skin (SPT), where mast cells are likely to be absent.

According to the AAAAI allergy guidelines,[24] a negative SPT should be followed by an ID test, at an allergen concentration of no less than 1:1000 weight/volume (wt/vol) of the allergenic extract. (Weight/Volume is a rough unit of concentration commonly used with allergenic extracts. At the present time, many allergens have been standardized so the number of allergy units per milliliter can be defined).

A negative SPT therefore does not exclude the possibility of the patient still being reactive to an injected allergen. A negative SPT can potentially be a false negative result and the tested allergen could still react to a more concentrated intradermal injection of 1:1000 wt/vol of the same allergen. Some studies support the ID test as being more sensitive than the SPT to diagnose reactivity to inhalant allergens [27-31] even studies by the main allergy community.[24 (statement 14),32]

If an SPT produces a large wheal, it is logical to assume that the patient is very reactive; but the opposite may not necessarily be true. If the patient is not very reactive and the SPT is negative, even the dilution of 1:1000 wt/vol may not be enough to demonstrate reactivity.

Another skin test, the Intradermal Dilutional Test or IDT (previously known as Skin End Point Titration or SET) uses multiple dilutions of each allergen.[33-35] The IDT is endorsed by the AAOA, PAAS and AAEM. Briefly, for each allergen to be tested, six successive serial five-fold dilutions of the allergen extracts are prepared. For allergen extracts that are available as 1:20 wt/vol, the six dilutions contain an allergenic concentration of: 1:100 for dilution #1; 1:500 for dilution #2; 1:2500 for dilution #3; 1:12,500 for dilution #4; 1:62,500 for dilution #5 and 1:312,000 for dilution #6.

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The sixth dilution is the weakest and contains an allergenic concentration of 1:312,000 wt/vol, which is much weaker than the 1:1000 wt/vol dilution advocated by the allergy guidelines. The first two dilutions of 1:100 wt/vol and 1:500 wt/vol contain allergen much stronger than the 1:1000 wt/vol dilution advocated by the allergy guidelines as the concentration for an ID to be injected after a negative SPT.[24]

Using multiple intradermal dilutions during skin testing (IDT) offers two advantages over the ID with one single dilution: safety and increased sensitivity: safety and sensitivity.

IDT enables the practitioner to diagnose patients that are very sensitive and therefore will react to small doses of allergen. Starting the skin injections with a weak concentration of the allergen (#6 dilution) adds a tremendous amount of safety to the test. Challenging a patient initially with the sixth dilution and gradually increasing the strength of the injected allergen is much safer than an injection of a concentration of 1:1000 wt/vol dilution of the same allergen after a negative SPT. This is why it is not surprising that the IDT proved to be very safe in a prospective study.[28]

IDT enables the practitioner to diagnose patients with low level of reactivity. These patients are not very sensitive. They require a much larger dose of allergen to elicit a skin reaction than offered by the prick test. Often, even an ID injection of 1:1000 wt/vol may be too weak to trigger a skin response, therefore eliciting a false negative result. Yet, the patient may react to an allergen dilution of 1:500 wt/vol (2nd dilution) or 1:100 wt/vol (1st dilution). (NOTE: Not all allergy practitioners use dilution #1 in their ID tests).

It has been argued that ID tests using these high concentrations of allergens identify patients with such low levels of clinical sensitivity, that these may be false positives. This is why test results obtained with the stronger concentrations of allergen are disregarded by many in the allergy community.[24 (summary statement 30),36]

From a clinical point of view, it is observed that patients who are "low reactors" (identified only by reactions to the stronger concentrations of dilutions #3, #2 or #1) may have significant allergic disease such as nasal allergies, asthma, chronic sinusitis, chronic otitis media or skin rashes. These patients will not be diagnosed using only a prick test, and, as explained above, often will be missed by a single dilution ID of 1:1000 wt/vol. This is of clinical significance as treating low reactor patients with immunotherapy leads to clinical improvement. This is obvious and commonly observed by practitioners that use these concepts, but there are few references in the literature to support this.[29]

**Practical Application from Testing an Allergy Patient with an IDT**

The information provided by the IDT enables mixing a vaccine whose composition will be in accordance to the level of reactivity for each allergen in each individual patient. For example, a patient's treatment serum might include dust mite allergen at a concentration corresponding to dilution #5 and mold allergen at a concentration of dilution #2. This allows starting immunotherapy treatment with safety but at the same time with efficacy. Patients treated with this technique develop clinical improvement soon after onset of treatment. Because the initial level of reactivity was determined for each allergen, dose advancement usually proceeds without major problems leading to a successful treatment of the different allergic conditions mentioned above.

Surveys of AAAAI allergists have found cases of mortality during testing or immunotherapy administration.[37,38] Patients with asthma are at higher risk for severe reactions during testing and immunotherapy based on that technique.[39-41] Fatalities from immunotherapy, although rare, are more common in asthmatics.[38,42]

A survey of the AAOA members who were using IDT reported no cases of mortality during testing or immunotherapy administration.[43] Other studies corroborate the safety profile of the IDT and immunotherapy administration based on results from over 4.2 million injections.[44]

A relatively common occurrence in an allergy practice is to see patients who, following SPT, were told they had allergic rhinitis and/or asthma and yet were only offered medical intervention. There is no need to do an allergy test in order to prescribe medications. A good history will help the practitioner to plan implementation of environmental control measures in addition to prescribing appropriate medications. The same observation is valid for the patient that less frequently had a combination of a SPT and a single dilution ID test or a blood test with only a few positive results: diagnosis is done and medication is prescribed. Perhaps this may reflect the experience of some allergists that after their patients had been treated for the few allergens discovered by SPT their symptoms responded poorly.

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Dr. Saporta completed his training in 1990 at Columbia Presbyterian Hospital in New York City. He is board certified in otolaryngology and has been a fellow of the American Academy of Otolaryngic Allergy (AAOA) since 2001. His private practice in Elizabeth, New Jersey, is heavily oriented to the management of allergic conditions. Interested in the use of oral vaccines since early in his practice, Dr. Saporta presented a protocol for sublingual immunotherapy at the 64th annual meeting of the AAOA that since then has been successfully used for the management of allergic rhinitis with or without asthma.

When IDT is utilized and additional "minor" allergens are detected and treated, improvement is then accomplished. Sometimes patients "need" the result of the test to convince them that they really have allergy. Ideally, testing should be reserved for those patients that may benefit from immunotherapy.

A classic example of this problem is the diagnosis "non-allergic rhinitis." In this case the SPT and the blood test are negative. The patient is offered avoidance of triggers and usual medications.[45] These cases are diagnosed as Local Allergic Rhinitis[46] or "Non-Allergic Rhinitis with Eosinophilia Syndrome (NARES)"[47]since both the SPT and the blood test are negative.

Advising patients to avoid triggers and administering medication may well keep the symptoms under control but will not treat the underlying inflammation that can end with airway remodeling, chronic otitis[48] and chronic sinusitis which may even require surgery after years of disease. When the clinical diagnosis of allergy by a trained physician does not match the test, the patient is usually deprived of the only treatment that can correct the underlying inflammation. Treating with immunotherapy carries risks, but immunotherapy is the only treatment modality that can change the reactivity level of the affected patient, leading to clinically significant improvement[14] or even cure of the underlying inflammation. It has been demonstrated that immunotherapy prevents the development of asthma.[49]

The essential key to making an accurate and thorough diagnosis of which allergens affect a patient is using a testing method that provides maximum sensitivity with a minimum of false positives while using safe testing techniques. This can only be accomplished with the IDT. The use of serial dilutions in the IDT allows for maximal safety during testing, and enables the practitioner to mix a vaccine that will be highly effective with the least chances of eliciting a reaction during treatment. The authors, like other practitioners from the societies mentioned above, (AAOA, PAAS and AAEM), use IDT and plan immunotherapy according to the results of this test. Patients are tested for dust, animal dander, pollens and molds. With this approach, the authors have treated allergy patients very successfully for many years.

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