

Controversies in Allergy: Intradermal Aeroallergen Skin Testing



Dennis K. Ledford, MD, and Richard F. Lockey, MD Tampa, Fla

INTRODUCTION

Medical tests are performed to help confirm or exclude a suspected clinical diagnosis. Diagnostic tests, with some exceptions, should not be used for random disease screening. Tests, in order to be helpful, need to be reproducible (precise), to have a low risk commensurate with the information obtained, and to be reproducible and validated in populations with or without the disease in question. The test should provide sufficient information to justify its cost. Specific tests, in general, have a highly positive predictability when the diagnosis is strongly suspected and sensitive tests the opposite, a highly negative predictability when the diagnosis is less likely. The purpose of this article was to discuss the pros and cons of performing intradermal skin tests (IDSTs) primarily to detect aeroallergen-specific-IgE sensitivity in subjects with negative prick-puncture skin test (PPST) results.

CLINICAL UTILITY OF INTRADERMAL AEROALLERGEN SKIN TESTING

IDSTs are performed by injecting 0.02 mL of a diluted allergen extract intradermally and subsequently evaluating the size of the specific-IgE-dependent wheal and flare reaction. The total allergen dose administered with IDST is several logs greater

than with PPST, although the dose may vary depending on the dilution of the injected allergen extract. In general, a concentration of the IDST is chosen to provide greater sensitivity than the PPST.

The IDST is used by the Bureau of Biologics of the Food and Drug Administration to standardize most allergen extracts both for diagnosis and for treatment, providing evidence of the precision and reproducibility of IDST.¹ With the exception of galactose- α 1,3-galactose allergy, the PPST is almost exclusively used for food testing primarily because the risk of inducing a systemic allergic reaction to a food is too great. The limited reactivity or concentration of galactose- α 1,3-galactose in mammalian meat likely results in positive food IDST results with negative PPST results in affected subjects.² These observations are not related to the clinical assessment of aeroallergen sensitivity but provide evidence for the sensitivity of IDST. The IDST has a log or more greater sensitivity than does the PPST to detect specific-IgE depending on the dilution of the allergen solution used. Thus, sensitivity to minor components of a complex allergen extract or nonstandardized extract may require an IDST to detect specific-IgE. IDST is valid in other situations, for example, to detect low levels of specific-IgE, such as with stinging insect or penicillin hypersensitivity.^{3,4} Thus, the IDST fulfills the major criteria of a useful test specified in the previous paragraph.

The greater sensitivity of IDST also makes it particularly reliable to exclude an allergy to a specific allergen. The challenge is that the greater sensitivity of the IDST makes it inappropriate to identify an allergic etiology for disease unless there is high pretest possibility or greater likelihood that relevant specific-IgE is present. However, the risk of inducing a systemic allergic reaction with IDST versus PPST is greater because a larger allergen dose is administered. Also, allergen extracts injected intradermally can be associated with “false-positive results” either secondary to an irritant reaction or to a low concentration of specific-IgE without clinical significance.

A major disagreement about the IDST is its validity or value in inhalant allergen assessment.^{5,6} This debate is primarily due to the previously stated high sensitivity of the test and determining the clinical significance of low levels of allergen-specific-IgE. In general, the level or concentration of specific-IgE does not correlate with severity of symptoms but does correlate with the likelihood of having symptoms upon exposure. Critics of the IDST argue that the high sensitivity reduces the positive predictive value of the test based on challenge responses.⁷ This has been confirmed in various group studies that show that a positive IDST result does not add to the accuracy of identifying allergic subjects with positive, single-day, relatively high-dose allergen challenges.⁷⁻⁹ Therefore, the critics argue that the IDST should not be used clinically to assess inhalant allergy because it is no more accurate than random chance to identify a positive

University of South Florida Morsani College of Medicine and the James A. Haley VA Hospital, Tampa, Fla

Conflicts of interest: D. K. Ledford is employed by the University of South Florida College of Medicine and the Veterans Administration; declares competing relationships with Wicker, Smith, O'Hara, McCoy, Ford (law firm) on the topic asthma death; Shook Hardy Bacon (law firm) on the topic drug allergy; and Saieva and Stine (law firm) on the topic metal allergy; has received consultancy fees from Genentech and AstraZeneca; is a speaker for TEVA, Boehringer Ingelheim, Genentech, and Novartis; is on the Editorial Board of *Annals of Allergy Asthma and Immunology*; is coeditor of *Asthma: Co-Morbidities, Co-existing Conditions and Differential Diagnosis*; is editor of *Allergens and Allergen Immunotherapy* of Informa; is volume editor of *Encyclopedia of Allergy, Immunology and Vaccines* for Springer; is coeditor of *Asthma and Allergy Basics* for Springer; and is a contributor for UpToDate. R. F. Lockey is employed by the University of South Florida College of Medicine. He has no conflicting relationships for this article. He is a consultant for ARS Pharmaceuticals, Inc, and is principal investigator on Shire Protocol DYAX 2930-04 and BioCryst Protocol BCX7353. He is coeditor of the *Journal of Investigational Allergology and Clinical Immunology*, *Asthma: Co-Morbidities, Co-existing Conditions and Differential Diagnosis*; and *Allergens and Allergen Immunotherapy* of Informa; is volume editor of *Encyclopedia of Allergy, Immunology and Vaccines* for Springer; and is also editor of *Impact*, a USF intramural journal review.

Received for publication May 14, 2018; revised July 25, 2018; accepted for publication August 9, 2018.

Corresponding author: Dennis K. Ledford, MD, University of South Florida Morsani College of Medicine and the James A. Haley VA Hospital, 13000 Bruce B Downs Blvd, VAR 111D, Tampa, FL 33613. E-mail: dledford@health.usf.edu.
2213-2198

© 2018 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2018.08.003>

*Abbreviations used**IDST*-intradermal skin test*PPST*-percutaneous prick skin test

challenge in subjects with negative prick skin test result.⁷ The corollary is that a positive test result is no better than chance in predicting response to allergen avoidance or allergen immunotherapy. Therefore, the critics argue that IDSTs should not be used in assessment of inhalant allergy.

Clinical tests are not used for research but to assess the health of an individual subject. Clinical IDSTs are not intended to be a stand-alone observation, but the information contained therein is to be integrated into personalized decision making based on the history, physical examination, other diagnostic tests, and clinical experience. These factors establish a pretest probability essential to effective clinical decision making. Individual components cannot be judged as independent information. All individuals in a cohort do not have the same pretest probability. In the day of more personalized medicine, IDST facilitates personalized decision making based on the context of the results.

For example, the 2 authors see patients who have symptoms consistent with an allergic etiology during the spring pollen season in Florida. They have negative PPST results to native tree pollens and a positive IDST result to oak pollen and react each spring of the year when the oak pollen is so predominant. One could argue that the symptoms are secondary to a nonidentified allergen; however, clinical research, observation, and knowledge of the local aeroallergens make that unlikely.

Another fallacy of decrying the IDST is that this ignores the value of excluding allergy. The reason IDST is the standard of care for insect allergy or drug allergy is that the burden is not to miss specific-IgE, because it places the subject at risk for subsequent exposure. The same may be true for inhalant tests in certain circumstances. A negative IDST result essentially excludes inhalant allergy, at least to the tested allergen, assuming the quality of test reagent is adequate.

A positive IDST result identifies specific-IgE but in and of itself does not confirm clinical allergy. However, if the pretest probability or suspicion of clinical allergy is high, for example, based on a history of suspected cat allergy, the presence of an IDST positive response to cat has potential clinical value. The fact that the specific value has not been determined in rigorous studies is no different than the reports of *in vitro* specific-IgE in various categories, with all categories noted as abnormal or exceeding the negative threshold. A positive IDST result exceeds the negative threshold and may be of value in specific situations. Implied is that the results cannot be interpreted as evidence of allergy on their own but must be part of individualized clinical decision making.

Another argument for the IDST is that IgE-mediated responses have both an immediate and late-phase response.¹⁰ Some individuals may have a minimal or no immediate response but yet have a late-phase response to continued allergen exposure. Early and late-phase responses are not always linked as evidenced by therapies affecting the late-phase response and clinical disease without affecting the early response.^{11,12} Speculation persists that low-level allergic sensitivity, as detected by IDST, could be associated with chronic disease. High-dose challenge studies rely on the recognition of an immediate positive response, generally

in the setting of the absence of current or chronic environmental exposure. Thus, the recognized phenomenon of priming, by which allergic subjects become more reactive to subsequent allergen exposure, is not addressed by progressive, single-day challenges. To state this in another way, priming and the gradual onset of symptoms may occur in subjects with low-level sensitivity only detected by IDSTs and not detected by PPSTs or single-day allergen challenges. Studies to demonstrate this are lacking. However, clinically, this appears to occur. Percutaneous testing pertains primarily to the subject who, for example, is cat-sensitive, walks into a cat-infested environment, experiences rapid-onset symptoms, and has to leave immediately. In contrast, other individuals exposed to cat on a chronic basis do not necessarily have an immediate response but experience only persistent symptoms, manifested mainly by the late-phase response and more chronic disease.

Another problem with most of the studies showing no value of IDST is the selection of subjects. Skin reactivity to allergen testing is affected by age, sun exposure, skin pigmentation, and location of the applied test.¹³ The percutaneous test performance may not be as reliable if factors that minimize skin test reactivity are present. In these circumstances, the IDST may be necessary to identify clinically relevant specific-IgE. The published studies showing lack of benefit of IDST have not excluded these possibilities encountered regularly in the clinic.

Finally, current allergy assessment uses allergen extracts that vary in potency and reliability. IDST may have a greater role to play in testing with allergen extracts of lower potency or if clinical symptoms are due to minor allergens in the allergen mix. If IDST is not used, the erroneous clinical conclusion is formed that allergy is not responsible for symptoms. The aforementioned studies showing no positive predictive value of IDST have used well-characterized or standardized allergen extracts.

In conclusion, IDST is precise, low cost, has minimal risk in experienced hands, and has high negative predictive value with a lower positive predictive value, at least for an immediate response to an aeroallergen. In an individual with high pretest probability, the IDST may add to diagnostic accuracy. None of the published trials has selected subjects specifically with high pretest probability of allergy to the specific allergen tested and challenged repeatedly. Therefore, it is short sighted and restrictive to deny this information to a clinician assessing an individual subject and formulating a long-term, personalized treatment program.

CLINICAL UTILITY OF PERCUTANEOUS AEROALLERGEN SKIN TESTING WITHOUT INTRADERMAL AEROALLERGEN SKIN TESTING

The most economical and reliable test to identify specific-IgE is a PPST. Numerous studies have validated its positive predictive value,^{6,8} enabling the clinician to forecast a potentially positive clinical response to allergen avoidance, allergen immunotherapy, or symptoms with challenge testing. Furthermore, PPSTs are safer and use less resources than IDST or *in vitro* testing.

The value of an individual test is based on low cost, ease of performance, reproducibility, safety, and in particular, reliability to predict patient outcomes. PPST fulfills these points and is valid and generally reliable. When the clinician encounters subjects with specific symptoms, the test used should help discriminate symptoms from one cause, for example, allergy,

versus other causes. Testing with IDST, which has greater sensitivity, can confuse the question because false-positive versus true-positive tests are just as likely when 20% to 40% of the population is capable of producing specific-IgE. There are many other reasons for allergic-like symptoms that can be pursued once the PPSTs are judged to be negative or irrelevant. Furthermore, the PPSTs are graded by assessment of size. This mitigates, to some extent, against a second, more sensitive test. In other words, greater positive predictive value is provided by a larger versus a smaller test result. The test is not simply positive or negative but permits assessment of degrees of positivity.

In conclusion, efficiency and optimal care are essential to provide quality medical care at the lowest cost. PPSTs meet the criterion for optimal care by providing sufficient, but not excessive or superfluous, information theoretically enabling treatment to yield highly positive results.

SUMMARY

Both PPST and IDSTs are reproducible and identify specific-IgE with a biologic response reflecting dermal mast cell degranulation. PPSTs for inhalant allergens are reliable and cost-effective and identify clinically relevant sensitivity. However, low levels of specific-IgE may not be identified by this testing method. Although there is some debate, specific-IgE does not correlate generally with severity of symptoms but does correlate with the probability of a clinical response. Negative IDST result to inhalant allergens virtually excludes a possibility of allergy contributing to clinical symptoms in individual subjects. A positive IDST result does not independently prove clinically relevant sensitivity but may be of value in specific clinical situations. These include high pretest probability of allergen sensitivity, testing with nonstandardized allergen extracts that have variable potency, and testing for sensitivity to minor components of a complex mixture of allergens. The absence of confirmed validity of IDST based on high-dose, single-day challenges does not prove a lack of value for this test. This is of particular clinical importance for chronic, lower dose allergen exposure or allergen exposure following priming in which the threshold for response may not be identified with single-day challenge studies. The converse is also true; it is not cost-effective nor appropriate to

perform IDST for all potential aeroallergens or without assessment of pretest probability by history and physical examination. This approach increases patient discomfort, cost, and risk, with little or no likelihood of modifying patient management. Thus, both the PPST and IDST have merit for individualized clinical decision making.

REFERENCES

1. Turkeltaub PC, Rastogi SC, Baer H, Anderson MC, Norman P. A standardized quantitative skin-test assay of allergen potency and stability: studies on the allergen dose-response curve and effect of wheal, erythema, and patient selection on assay results. *J Allergy Clin Immunol* 1982;70:345-52.
2. Commins SP, Santinover SM, Josen J, Mozena J, Borish L, Lewis BD, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose- α -1, 3-galactose. *J Allergy Clin Immunol* 2009;123:426-33.
3. Budd MA, Parker CW, Norden CW. Evaluation of intradermal skin tests in penicillin hypersensitivity. *JAMA* 1964;190:203-5.
4. Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, et al. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol* 2017;118:28-54.
5. Lindblad JH, Farr RS. The incidence of positive intradermal reactions and the demonstration of skin sensitizing antibody to extracts of ragweed and dust in humans without history of rhinitis or asthma. *J Allergy* 1961;32:392-401.
6. Wood RA, Phipatanakul W, Hamilton RG, Eggleston PA. A comparison of skin prick tests, intradermal skin tests, and RASTs in the diagnosis of cat allergy. *J Allergy Clin Immunol* 1999;103:773-9.
7. Oppenheimer J, Nelson HS. Skin testing. *Annals Allergy Asthma Immunol* 2006;96:S6-12.
8. Nelson HS, Oppenheimer J, Buchmeiera A, Kordash TR, Freshwater LL. An assessment of the role of intradermal skin testing in the diagnosis of clinically relevant allergy to timothy grass. *J Allergy Clin Immunol* 1996;97:1193-201.
9. Schwindt CD, Hutcheson PS, Leu SY, Dykewicz MS. Role of intradermal skin tests in the evaluation of clinically relevant respiratory allergy assessed using patient history and nasal challenges. *Ann Allergy Asthma Immunol* 2005;94:627-33.
10. Leaker BR, Malkov VA, Mogg R, Ruddy MK, Nicholson GC, Tan AJ, et al. The nasal mucosal late allergic reaction to grass pollen involves type 2 inflammation (IL-5 and IL-13), the inflammasome (IL-1 β), and complement. *Mucosal Immunol* 2017;10:408-20.
11. Metzger WJ, Hunninghake GW, Richerson HB. Late asthmatic responses: inquiry into mechanisms and significance. *Clin Rev Allergy* 1985;3:145-65.
12. Ong YE, Menzies-Gow A, Barkans J, Benyahia F, Ou TT, Ying S, et al. Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. *J Allergy Clin Immunol* 2005;116:558-64.
13. King MJ, Lockey RF. Allergen prick-puncture skin testing in the elderly. *Drugs Aging* 2003;20:1011-7.

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.