

The role of intradermal skin testing in inhalant allergy

Christopher W. Calabria, MD, and Larry Hagan, MD

Objective: To provide an overview of the role of intradermal skin testing (IDST) in inhalant allergy.

Data Sources: A literature search was conducted in MEDLINE to identify peer-reviewed articles related to IDST using the following keywords: *skin testing*, *intradermal*, *intracutaneous*, *aeroallergen*, and *inhalant allergen*. In addition, references cited within these articles were also reviewed.

Study Selection: Articles were selected based on their relevance to the topic.

Results: The use of IDST for inhalant allergy varies widely among allergists. When performed, it is necessary to use a 100- to 1,000-fold dilution from the stock allergen extract. IDST is used routinely in the standardization of extracts in the United States. With a negative skin prick test result, a positive IDST result has low agreement with in vitro and challenge results and generally adds little to the diagnostic evaluation. In contrast, a negative IDST result generally has a high negative predictive value. Only a few inhalant allergens have been evaluated with challenge models for IDST. A summary of the data is also presented in tabular form.

Conclusions: Most of the literature suggests that with a negative skin prick test result, a positive IDST result adds little to the diagnostic evaluation of inhalant allergy. However, additional studies are necessary using challenge models for less potent and nonstandardized inhalant allergens (molds, trees, dog, weeds).

Ann Allergy Asthma Immunol. 2008;101:337–347.

Off-label disclosure: Drs Calabria and Hagan have indicated that this article does not include the discussion of unapproved/investigative use of a commercial product/device.

Financial disclosure: Dr Calabria has served as a speaker for Phadia Inc.

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INTRODUCTION

Introduced by Cooke in 1911, intradermal skin testing (IDST) has played an integral role in the diagnostic evaluation of allergic disease. Since its inception, the clinical application and diagnostic accuracy of IDST have been challenged, and its use varies widely. The current practice parameter recommends IDST when increased sensitivity is the main goal of testing.¹ This is valuable in penicillin and venom hypersensitivity but unnecessary in food allergy in which skin prick tests (SPTs) are highly sensitive and IDSTs potentially dangerous.¹ The IDST is also useful in the evaluation of suspected hypersensitivity reactions to insulin, heparin, muscle relaxants, and chemotherapeutic agents.

The biggest area of controversy surrounds the use of the IDST in inhalant allergy. The IDST for inhalant allergy may

be helpful when the SPT result is negative despite a compatible exposure history. Also, sensitivity to low-potency aeroallergen extracts may best be evaluated by an IDST. By gaining sensitivity, however, the test loses specificity. The correlation between IDSTs and inhalation challenge tests is generally lower than for SPTs.^{2–8} A clear distinction between an irritant reaction and true sensitization is more difficult to obtain with IDSTs, and there are more safety concerns.⁹

The application of IDSTs for aeroallergens varies widely, as highlighted by a recent survey of allergists.¹⁰ The number, concentration, and criteria for a positive IDST result differed considerably. The IDST was used by 85.2% of 539 respondents. The average number of IDSTs performed ranged from 2.03 (grasses) to 5.6 (perennial), with ranges of 0 to 49 (perennials), 0 to 23 (trees), 0 to 11 (grasses), 0 to 24 (weeds), and 0 to 35 (molds). The extract concentrations used for IDSTs were diverse (dilutions from concentrated extract): 20.8% use 1:100 dilutions, 10.3% use 1:500 dilutions, and 59.4% use 1:1,000 dilutions. The criteria for defining a pos-

Affiliations: Department of Allergy and Immunology, Wilford Hall Medical Center, Lackland AFB, Texas.

Received for publication July 11, 2008; Accepted for publication August 15, 2008.

itive IDST result varied from a wheal 3 mm or larger than the negative control (55.2%) to a wheal 5 mm or larger than the negative control to a wheal equal or larger than the histamine control (18%).

THE IDST

An IDST involves injecting 0.02 to 0.05 mL into a superficial layer of dermis to make a 2- to 3-mm bleb. Tests are read at 10 to 15 minutes. SPTs should always precede IDSTs. Factors that affect IDSTs are similar to those that affect SPTs (eg, medications, area of body).¹¹ The IDST histamine control (0.1 mg/mL) should be weaker than the SPT histamine control (1 mg/mL). Both bevel-up and bevel-down methods can be used. Although the recent practice parameter¹ does not comment on this issue, Howard et al¹² compared these 2 methods and found that the bevel-down method performed quicker, resulted in less bleeding and squirting solution into the air, and led to more successful bleb formation and higher comfort rate.

WHAT IS A POSITIVE IDST RESULT?

Definitions for a positive aeroallergen IDST result are variable, and evidence-based studies on grading of IDST results are lacking. Different measures, such as longest diameter, sum of longest diameter and its orthogonal diameter, a wheal 6 mm or larger with "surrounding erythema," a wheal 3 mm or larger than the negative control, and any response greater than the negative control, are used. The semiquantitative grading system of Norman specified a minimum cutoff for an IDST to be a wheal of 5 to 10 mm with a erythema diameter of 11 to 20 mm or 21 to 30 mm. The 11- to 20-mm erythema diameter was associated with a 3- to 5.9-mm wheal, and a 21- to 30-mm erythema diameter was associated with a 6- to 9-mm wheal.¹³

McCann and Ownby¹⁴ demonstrated the inconsistency of allergists in scoring and interpreting skin test results. Physicians were asked to score and interpret a series of skin tests and decide if they desired a follow-up IDST. The most agreement was found in those test results rated as 4+, and the highest variation was found among those scored 1+ or 2+. Seven of 33 respondents requested IDSTs on all negative SPT results. The number of IDSTs requested ranged from 0 to 11 (of 22 test items), with an average of 3.5. This study illustrated the wide variation in both the scoring and use of IDSTs.

IDST wheals and erythema are generally believed to have significantly higher reproducibility than the SPT. Gottlieb,¹⁵ however, found suboptimal reproducibility of IDSTs on 33 atopic patients performed in duplicate at 2 different visits an average of 6 months apart. Tests were in agreement 87% of the time at the same visit. Pollens, epidermal agents, and molds had more reproducible results than food allergens. They demonstrated a 27.2% discrepancy rate using 5 mm as positive, whereas reanalysis of the data using 10 mm as positive improved the reproducibility of testing to 95% (5%

discordance). In contrast, other studies have shown good precision using different IDST methods.¹⁶

One distinct advantage of IDST is that it provides accurate and precise data in extract standardization. The IDST is used in defining the D_{50} (intradermal dilution for 50-mm diameter of erythema determines the bioequivalent allergy units), which is the dilution of an allergen yielding the sum of the erythema diameters that equal 50 mm. The mean D_{50} for 15 highly allergic individuals is used to determine the D_{50} for the extract. Erythema is used because it has a steeper-dose response curve at the end-point dilution, which gives more accurate and precise results when discriminating different allergen doses.¹³ Therefore, the IDST can signify cell-bound allergen specific IgE and not merely irritant responses.

Similarly, Van Metre et al¹⁷ showed that a decrease in skin sensitivity to cat extract was demonstrated by IDST and SPT methods after 1 year of immunotherapy. Twenty-two patients with cat-induced asthma were randomized to either cat immunotherapy or placebo. After 1 year of treatment, patients undergoing immunotherapy had a significant increase in the intradermal dose of cat extract required to produce both a wheal 10 mm or larger (with erythema diameters of 20 to 30 mm) and mean erythema diameter of 20 mm.

Using purified major allergens, Wittemann et al¹⁸ showed that with similar radioallergosorbent test (RAST) levels, the amount of allergen required for a positive SPT result may differ by as much as a factor of 100 among patients. They concluded that this was not due to imprecision of either the RAST or SPT. Thus, some patients may require IDSTs to yield positive results even though their serum specific IgE level is similar to patients with a positive SPT result at 1:10 wt/vol. These studies suggest a role for the IDST in inhalant allergy.

IDST CONCENTRATIONS

A wide variety of IDST concentrations are in use. At our institution, we use a 100-fold dilution (1:1,000 wt/vol) from the SPT extract (generally, 1:10 wt/vol or 1:20 wt/vol). The practice parameter recommends that the starting dose of an IDST extract should range from 100- to 1,000-fold dilutions of the concentrated extract used for SPT.¹ Comparative testing between SPTs and IDSTs suggests that SPTs require 10 to 30,000 times more allergen.

Stenius¹⁹ published a comparative study of the IDST and SPT in dust mite allergy. Most patients who reacted on SPTs to 10^{-2} g/mL reacted correspondingly on IDSTs to 10^{-5} g/mL. Therefore, the IDST needed to be 1,000 times weaker to elicit a similar reaction. Also, as higher IDST concentrations were used, almost all patients were positive. The IDST correlated best with the RAST at 10^{-5} g/mL.

Indrajana et al²⁰ compared IDST to scratch and SPT in grass and dust allergy and found that IDST was 500 to 1,500 times more sensitive than scratch testing and approximately 1,000 times more sensitive than the SPT. Perera et al²¹ studied RAST vs IDST in ragweed pollinosis at varying concentrations. A positive IDST result at lower concentrations (10^{-8} to

10^{-6} g/mL) correlated better with history (68%–72.7%) and RAST (44%–55%) than a positive IDST result at higher concentrations (10^{-5} to 10^{-3} g/mL). Agreement between the IDST and RAST was maximal at the lowest concentration of 10^{-8} g/mL (55%).

In a study by Neimeijer et al^{22,23} aimed at optimizing sensitivity and specificity, best performance was obtained when timothy and dust mite were diluted 10-fold for the SPT and 1,000-fold for the IDST. Murphree and Kniker²⁴ concluded that IDST concentrations of 1:1,000 and 1:1,500 wt/vol agreed closely with an SPT result of 1:10 or 1:20 wt/vol (100-fold weaker), whereas stronger concentrations (1:500 wt/vol) were more often positive and weaker concentrations (1:4,500 wt/vol) more often negative. Malling²⁵ determined that the median wheal of the IDST is 30 times larger than that of the SPT in a group of mold allergic asthmatic patients and calculated that the IDST requires approximately 500 times (range, 20–4,000) more dilute extract than SPT.

Therefore, most studies, consistent with the practice parameter, demonstrate that a 100- to 1,000-fold dilution from the prick extract should be comparable when performing the IDST (Table 1). With a 100-fold dilution (1:1,000 wt/vol extract), the IDST will have higher sensitivity but lower specificity.

SAFETY

Several large studies have demonstrated that the SPT is extremely safe,^{9,26–28} which is well documented in a recent review.²⁹ A cross-sectional population study showed an adverse reaction rate of 0.04% ($n = 16,204$),²⁶ whereas a 1-year survey of 1,144 patients receiving SPTs and selective IDSTs revealed a 6% systemic reaction rate.²⁷ In a 10-year retrospective questionnaire-based analysis of fatalities from skin testing and immunotherapy, Lockey et al²⁸ reported that 5 of 6 SPT fatalities were associated with IDSTs without prior SPTs and 5 of 6 patients had asthma. A more recent 12-year survey (1990–2001) revealed no skin testing fatalities to inhalant allergens.⁹ Thus, aeroallergen skin testing is very safe, particularly if IDSTs are only performed after a negative SPT result is found.

IDSTs IN NONALLERGIC INDIVIDUALS

An effective diagnostic test should distinguish allergic from nonallergic individuals. In 1935, Rackemann and Simon³⁰ tested 60 nonallergic patients with IDSTs to 9 allergens. They discovered a large number of positive results, ranging from 1.6% for feathers to 20% for ragweed. In 1936, Grow and Herman³¹ studied 150 nonallergic patients with IDSTs to 13 allergens. Most patients (55.5%) reacted to 1 or more extracts; sensitization to specific allergens ranged from 4.6% (egg) to 38.6% (horse). Likewise, Lindbladd and Farr³² reported a high incidence (17%–50%, depending on the allergen) of positive IDST reactions in 100 nonallergic patients, particularly at the strongest concentration.

Efron and Boatner³³ drew a different conclusion after studying 80 controls and 45 patients with fall hay fever who received IDSTs of ragweed extract ranging from 0.02% to 0.0000001%. More hay fever patients had positive IDST results at each extract concentration, and few controls tested positive. Diagnostic efficiency was 90% to 97% overall, and stronger extract concentrations were positive in more than 95% of allergic patients. They concluded that a positive IDST result indicates true allergy.

Overall, the preponderance of evidence demonstrates a high rate of positive IDST results in nonallergic asymptomatic individuals, particularly at higher concentrations (Table 2). Notably, these studies were published from 1935 to 1961, before extract standardization, reliable antigen purity, and more sensitive serum specific IgE testing, which may limit their current relevance.

CLINICAL RELEVANCE OF THE IDST WHEN THE SPT RESULT IS NEGATIVE

In clinical practice, most allergists want to know the value of performing an IDST if the SPT result is negative. The following studies examine the scenario (Table 3) of when IDSTs were only performed if a preceding SPT result were negative and used either history or RAST as the gold standard. The ideal gold standard would be to compare the IDST result to direct allergen challenge results (Table 4) because history is

Table 1. Summary of Studies That Evaluated Different Concentrations of IDSTs and Their Relation to SPT Reactivity

Study	No. of study participants	SPT	RAST	IDST	Allergens	Results
Stenius ¹⁹	31 Allergic and 10 controls	Yes	Yes	Yes	Dust mite	10^{-2} SPT = 10^{-5} g/mL IDST 10^{-5} IDST g/mL = best RAST agreement
Indrajana et al ²⁰	26	Yes	No	Yes	Grass, DM	SPT:IDST 1:380 for grass SPT:IDST 1:1,500 for DM
Perera et al ²¹	4 Groups of >400	Yes, scratch	Yes	Yes	Ragweed	Positive IDST at low concentration (10^{-6} to 10^{-8}), better correlation with RAST
Neimeijer ²²	41	Yes	Yes	Yes	Timothy, DM	1:10 for SPT and 1:1,000 wt/vol for IDST optimal with best sensitivity/specificity
Murphree and Kniker ²⁴	3 Groups	Yes	No	Yes	6–11 Allergens	IDST at 1:1,000 and 1:1,500 wt/vol correlated best with SPT

Abbreviations: DM, dust mite; IDST, intradermal skin test; RAST, radioallergosorbent test; SPT, skin prick test.

Table 2. Summary of Studies That Investigated IDSTs in Nonallergic Patients

Study	No. of study participants	Allergens	Positive criteria	Results
Rackemann and Simon ³⁰	60 Nonallergic	9	Irritable skin	High percentage of positive results
Grow and Herman ³¹	150 Nonallergic	13	>5-mm wheal and >15-mm flare	55.5% positive
Lindblad and Farr ³²	100 Nonallergic	5 RW, DM	>5-mm wheal	0.001 mg n/mL: 1%–4% positive; 0.1 mg n/mL: 17%–50% positive; IDST not useful
Efron and Boatner ³³	80 Control and 45 fall hay fever	Ragweed	Positive, doubtful, or negative	Higher percentage in hay fever patients at each concentration, believe IDST is useful

Abbreviations: DM, dust mite; IDST, intradermal skin test; RW, ragweed.

Table 3. Summary of Studies That Investigated the Clinical Relevance of IDSTs When the SPT Result Is Negative^a

Study	No. of study participants	SPT (wt/vol) ^b	Allergens	Positive criteria	Results
Collins and Bremner ³⁵	50	1:10	12	Unknown	Comparison of SPT and IDST to RAST: Agreement: (1) SPT and RAST, 82.7%; (2) IDST and RAST: 66.5%; (3) positive IDST and RAST results, 7%; (4) IDST NPV, 99.4%
Pascual et al ³⁶	312	1:50	66	Unknown	Comparison of SPT and IDST to RAST: (1) positive SPT and RAST results, 45%–81% agreement; (2) positive IDST and RAST results, 0%–4.9% agreement; (3) NPV, 97.6% (grasses), 96.8% (weeds), 99.3% (trees), 98.5% (molds), and 99.0% (dust mite, house dust)
Brown et al ³⁷	311	1:20, 1:10	14 SPT, 6 IDST	Any reactivity and >5 mm	Gold standard: clinical history and comparison to RAST; IDST not related to history or RAST; more often positive in nonallergic patients
Williams et al ³⁸	181	1:10 to 1:100	5	4+ >12 mm 3+ > 8 mm	Gold standard: clinical history; IDST increases timothy efficiency by 3%–4%; decreased specificity and RAST positivity with IDST
Chinoy et al ³⁹	118	1:10	DM, CR, cat, dog	>2+	Comparison of SPT and IDST to RAST: (1) 52%–62% concordance overall; (2) DM, cat: positive IDST result decreased agreement with RAST; (3) dog, CR: positive IDST result slightly increases agreement with RAST; (4) negative IDST result increases percentage of negative RAST result by 5%–10%

Abbreviations: CR, cockroach; DM, dust mite; IDST, intradermal skin test; NPV, negative predictive value; RAST, radioallergosorbent test; SPT, skin prick test.

^a There were no challenges performed in this group of studies.

^b All IDST concentrations were 1:1,000 wt/vol.

subjective and insufficient alone to define the performance characteristics of specific IgE testing.^{19,34}

Collins-Williams and Bremner³⁵ compared the SPT (1:10 wt/vol), IDSTs (1:1,000 wt/vol), and RASTs in 50 atopic

patients with 12 allergens. Correlation between SPTs and RASTs was 82.7%. Inclusion of IDSTs reduced the agreement to 66.5%. Only 7% of positive IDST results were associated with a positive RAST result. Thus, 93% of positive

Table 4. Clinical Relevance of IDSTs When the SPT Result Is Negative in Studies That Used Provocation Testing as the Gold Standard

Study	No. of study participants	SPT (wt/vol)	IDST (wt/vol)	Allergen	Challenge	Result
Berg and Johansson ²	118	1:10	1:1,000	6	Nasal bronchial conjunctival	Agreement with provocation testing: (1) SPT, 76%, 92% if $\geq 3+$; (2) RAST, 77%; Agreement with provocation testing: (1) negative SPT result, positive IDST result, and positive RAST result: 88%; (2) negative SPT result, positive IDST result, and negative RAST result, 31%; (3) compared with provocation test: NPVs: IDST, 80%; SPT, 66%; RAST, 71%
Reddy et al ³	34 With positive and negative controls	1:10, 1:50	1:1,000	60	Nasal challenge	(1) Negative SPT results and positive IDST result: 0 positive RAST result and LHR result, 1 positive NP test result; (2) 19 positive SPT results: 63% positive RAST results, 89% positive LHR results, 89% positive NP results; (3) negative controls: no positive RAST, LHR, or NP results; (4) NPV of IDST: 97% vs NP, 100% vs LHR
Stenius et al ⁴	95	Yes	Yes	DM, grass	Nasal challenge	In patients with negative SPT results: (1) DM: 13/14 positive IDST results, 2/14 positive RAST results, and 2/9 positive nasal challenge results; (2) grass: 2/9 positive IDST results, 2/9 positive RAST results; (3) IDST added little to SPT results: sensitivity, 62%; specificity, 89%; IDST: sensitivity, 17% (0% cat, 36% DM) vs history; no positive challenges in negative SPT result and positive IDST result group
Schwindt et al ⁵	97	1:20	1:1,000	6	Nasal challenge	IDST: sensitivity, 0%–60%; specificity, 31%–32%; PPV, 0%–23%; NPV, 77%–92%, efficiency, 31%–39%; NPV similar to NPV for SPT and RAST
Wood et al ⁶	120	10,000 BAU/mL	100, 1,000 BAU/mL	Cat	Cat challenge	IDST: sensitivity, 100%; specificity, 35%–65%; PPV, 41%–56%; NPV, 100%; SPT with better specificity and PPV but IDST with higher sensitivity and NPV
Sharma et al ⁷	69	1:10	1:1,000 1:100	Mouse	Mouse challenge	Negative SPT result and positive IDST group: 11% agreement with challenge, 22% with symptom and pollen counts; positive IDST result after negative SPT result not significant; NPV of IDST, 89%
Nelson et al ⁸	4 Groups	10,000, 100,000 AU/mL	1,000 AU/mL	Timothy	Grass challenge	

Abbreviations: DM, dust mite; IDST, intradermal skin test; LHR, leukocyte histamine release; NP, nasal provocation; NPV, negative predictive value; PPV, positive predictive value; RAST, radioallergosorbent test; SPT, skin prick test.

IDST results were associated with negative SPT and RAST results and were likely clinically insignificant. Pascual et al³⁶ came to similar conclusions regarding IDSTs in 312 patients with 66 aeroallergens.

Brown et al³⁷ reported on a group of 311 patients selected from an epidemiologic study in Tucson, Arizona, using history as the gold standard. Significant overall agreement was observed between the presence of SPT reactivity and respiratory allergy history (77.7% vs 58.0%), particularly for reactions of 5 mm or larger (61.1% vs 34.0%). In contrast, in patients with negative SPT results, a greater prevalence of positive IDST results was present among patients with no allergy history than among those with symptoms (49.2% vs 39.3%). More patients in the asymptomatic group had IDST reactions of 5 mm or greater (12.7% vs 6.1%); the only allergen to have significantly more positive IDST results in the allergic group was careless weed. Positive SPT results in both groups correlated with higher RAST levels, but no relationship was found between positive IDST and RAST results. For Bermuda grass, the overall agreement between SPTs and RASTs was 89.2%, whereas only 4% of positive IDST results had a positive RAST result. They concluded that IDST results were unrelated to allergy symptoms or IgE.

Williams et al³⁸ evaluated SPTs and 3 different in vitro assays for timothy grass, short ragweed, *Alternaria*, cat, and *Dermatophagoides farinae* using history diagnosis as the gold standard. IDSTs were performed if the SPT result was 1+ or less and sometimes if the SPT result was 2+. For timothy grass, the greatest efficiency (by 3%–4%) was obtained when the SPT was supplemented with an IDST. For cat, the addition of an IDST increased sensitivity without loss of specificity only when a 4+ was considered positive; if a 3+ reaction was positive, there was loss of specificity (67%). The addition of a positive IDST result was more commonly associated with negative in vitro results for all 3 assays.

Chinoy et al³⁹ studied the SPT, IDST, and RAST (Phad-eas) for indoor allergens in 118 patients. Overall, this study demonstrated moderate concordance between skin testing and RAST, with agreements of 52.2% (dog) to 62.2% (cat). The addition of a positive IDST result in this study reduced agreement with RAST for cat and dust mite, whereas it increased agreement for cockroach from 15% to 22% and for dog from 7% to 16%. A negative IDST result increased the likelihood of a negative RAST result by 5% to 10%.

NEGATIVE SPT AND POSITIVE IDST RESULTS COMPARED WITH PROVOCATION TESTS

Another group of studies compare the IDST and SPT to provocation tests (Table 4). Again, IDSTs are performed only when the SPT result is negative. Berg and Johansson² studied 118 children with SPTs, IDSTs, RASTs, and provocation tests. The correlation of all positive SPT results with positive provocations was 76%, but it was not until the SPT result was 3+ that agreement increased to 92%. In contrast, of patients with a positive IDST result, a negative SPT result, and a negative RAST result, only 31% had a positive provocation

test result. In patients with a positive IDST result, a negative SPT result, and a positive RAST result, 88% had a positive provocation test result. Conversely, in patients with a negative IDST result, a negative SPT result, and a negative RAST result, 80% had a negative provocation test result. Thus, a positive IDST result in an SPT-negative patient had low correlation with provocation testing unless the RAST result was positive, whereas a negative IDST result had a higher negative predictive value (80%) than SPT (66%) or RAST (71%).

Reddy et al³ studied 34 patients with perennial rhinitis symptoms who tested negative to an SPT panel of 60 allergens but positive on IDST and had them undergo RAST, nasal provocation, and leukocyte histamine release tests. None had positive RAST or leukocyte histamine release results, and only 1 had a positive nasal provocation result. Of 19 positive controls (positive SPT result), 12 had positive RAST results, 17 had positive leukocyte histamine release results, and 17 had positive nasal provocation results. Of 13 negative controls, none had a positive RAST, leukocyte histamine release, or nasal provocation result, but 3 had positive IDST results. These authors concluded that when SPT results are negative in patients with perennial rhinitis, positive IDST results are not likely to indicate true allergy. Stenius et al⁴ also found that when preceded by a negative SPT result, a positive IDST result infrequently correlates with positive nasal challenges and RAST results.

Using nasal challenges, Schwindt et al⁵ studied the relative value of the epicutaneous (SPT), percutaneous (Multi-Test II; Lincoln Diagnostics, Decatur, Illinois), and IDST methods compared with patient history for 6 common allergens. Compared with patient history, sensitivities overall were 77% (Multi-Test II) and 62% (SPT), whereas specificities were 89% (SPT) and 84% (Multi-Test II). In contrast, compared with history, the sensitivity for IDST was only 17%. The IDST reproducibility was low, because 6 of 8 patients who initially fit the negative SPT result and positive IDST result profile had a negative IDST result on subsequent testing. Nasal challenge results for the negative SPT result and positive IDST result group were similar to the negative control group, and no challenges were positive. In the positive control group (relevant positive SPT result), nasal challenge results were significantly more positive.

Wood et al⁶ compared SPT, IDST, and RAST in the diagnosis of cat allergy using a cat challenge model. Of patients with positive SPT results, 89% had a positive upper respiratory tract response and 90% a positive lower respiratory tract response to cat challenge. Patients with negative SPT results (n = 39) were just as likely to have a positive challenge with a negative IDST result (31%) as a positive IDST result (24%). No relationship was found between challenge result and IDST wheal size or whether the patient was positive at 100 vs 1,000 BAU/mL. On the basis of challenge results, the sensitivity, specificity, positive predictive value, negative predictive value, and efficiency were high for the SPT and RAST but low for the IDST (sensitivity, 0%–60%;

specificity, 31%–32%; PPV, 0%–23%; NPV, 77%–92%; and efficiency, 31%–39%). They concluded that the IDST added little to the diagnostic evaluation of cat allergy. The same group had similar conclusions for the mouse IDST compared with the SPT, although the IDST had high sensitivity and negative predictive value (with low sensitivity and positive predictive value) in this nasal challenge model.⁷

Nelson et al⁸ studied the role of the IDST in timothy grass allergy. They performed detailed histories, SPTs, IDSTs, nasal challenges, and correlation of daily symptoms and medication use with daily pollen counts. A positive SPT result was a 3-mm wheal or greater with a erythema diameter greater than 5 mm. A positive IDST result was a 6-mm wheal or greater with erythema. There were 4 groups. Group 1 had a positive history, negative SPT result, and positive IDST result (n = 9). Group 2 had a positive history and positive SPT result (positive control group, n = 22). Group 3 had a positive history and negative SPT and IDST results (negative control group, n = 19). Group 4 had a negative history, SPT result, and IDST result and an IgE level less than 20 IU/mL (nonallergic control group, n = 18). On the basis of nasal challenge, timothy pollen allergic reactions were noted in 11% of group 1, 68% of group 2, 11% of group 3, and 0% of group 4. On the basis of symptom correlation with pollen counts, 22% of group 1, 64% of group 2, 21% of group 3, and 0% of group 4 were considered allergic. On the basis of both criteria, the percentage of positive responses was 0% for group 1, 46% for group 2, 0% for group 3, and 0% for group 4. Thus, the presence of a positive IDST result after a negative SPT result to timothy grass was not clinically significant. This true-positive rate of 46% was similar to true-positive rates reported for gold standard challenges in insect sting (60%), latex (50%), and food allergy (<50%).¹³

Therefore, a positive IDST result in an SPT-negative patient will agree with the RAST result approximately 5% to 10% of the time and correlate with history and provocation testing in only a few instances. This is especially true when using more potent or standardized extracts. For these allergens (cat, timothy) at these concentrations, the IDST adds little to the evaluation. However, a negative IDST result generally has high negative predictive values in ruling out IgE-mediated allergy. In addition, what remains unanswered is the relevance of IDST with less potent or unstandardized aeroallergens, such as molds or trees.

THE ROUTINE USE OF THE IDST IN INHALANT ALLERGY

The aforementioned studies indirectly measure IDST performance because they are not performing IDSTs routinely (Table 5). SPT-negative patients are a select population, and thus one would not expect high correlation from the IDST. If the IDST is performed on all patients, however, the tests perform better. Menardo et al⁴⁰ compared 3 different SPT methods with the IDST and RAST (Phadebas) in dust mite allergy. Thirty patients 12 to 66 years old were included based on a positive IDST result. The IDST gave only 2

false-positive reactions (positive IDST with negative SPT and RAST results) because 28 of 30 patients also had evidence of specific IgE by SPT or RAST. In 10 control patients with negative IDST results, all skin testing methods and RASTs produced negative results. Ownby and Bailey⁴¹ studied the reactions of 20 patients ages 4 to 20 years to 23 antigens. Of the 4 patients who were SPT negative and IDST positive, all had positive RAST results. The authors concluded that the IDST was more sensitive.

Mariotta et al⁴² studied 64 patients with SPT, IDST, and AllergEns (in vitro) testing to 8 allergens. There was positive or negative concordance (ie, all 3 positive or negative) in 64.1% of tests. In 101 instances, the SPT and IDST results disagreed. Most (99/101) involved a negative SPT result and a positive IDST result, and only 34% of the time was the AllergEns result positive.

Ahlstedt et al⁴³ performed routine IDSTs, RASTs, and provocation tests on 65 atopic patients and found 85% correlation between in vivo and in vitro testing for timothy, birch, and dog. Brusasco et al⁴⁴ studied the use of routine IDSTs and SPTs and compared them with RASTs and bronchial provocation tests in 384 atopic patients. Overall, positive SPT and RAST results (82%) correlated better than positive IDST and RAST results (68%). Positive IDST results to tree pollens (80%), dandruffs (70%), and molds (85%) showed higher rates of agreement with RAST results than those performed for *Parietaria* (62.5%), *Compositae* (33%), and dust mite (62.1%). A negative IDST result correlated well with a negative RAST result (75.8%), but negative SPT and negative RAST results were better (81.2%). There was better agreement between positive SPT and bronchial provocation test results (54.5%) than between positive IDST and bronchial provocation test results (42.8%). Escudero et al⁴⁵ studied the cost-effectiveness of various methods of diagnosing *Alternaria* hypersensitivity in rhinitis and asthma patients with routine IDSTs, SPTs, Phadezyme RASTs, and challenges (nasal, bronchial, conjunctival). The gold standard used was positive history plus positive nasal or bronchial challenge. Overall, the conjunctival challenge, IDST, and SPT (94% to 100%) were the most sensitive tests, with similar specificity (94%), and the IDST performed well.

Therefore, the routine use of the IDST shows better but still only moderate concordance with RAST and challenge results, and the SPT is still superior. A recent evidence-based review on diagnostic testing for allergic rhinitis calculated likelihood ratios for the IDST for several studies; most likelihood ratios were near 1.0, meaning the IDST generally is clinically insignificant in changing disease probability.⁴⁶ The exception was the aforementioned *Alternaria* IDST study, where the likelihood ratio was 8.8, suggesting that the IDST may have a role in the diagnosis of *Alternaria* hypersensitivity.

COMPARING THE IDST WITH RAST

Some studies focused on comparing IDST to RAST (Table 6). SPTs were not routinely performed. Tang and Wu⁴⁷

Table 5. Clinical Relevance of Routine IDSTs in Inhalant Allergy

Study	No. of study participants	SPT (wt/vol)	IDST (wt/vol)	Allergens	Positive criteria	Results
Menardo et al ⁴⁰	30	3 types	1:10,000	DM		Compared IDST with 3 types of SPT and RAST, no challenges done; IDST more sensitive than SPT; NPV, 100% (10/10)
Ownby and Bailey ⁴¹	20	1:20	1:1,000	23	Unknown	Of 4 positive IDST results and negative SPT results, all with positive RAST results
Mariotta et al ⁴²	64	50,000 SBE/mL	500 SBE/mL	8	Larger than positive control	Compared IDST with SPT and RAST; 64.1% concordance; 99/161 discrepancies: negative SPT result and positive IDST result; only 34% of these positive RAST results
Ahlstedt et al ⁴³	65	1:10	Not stated	Timothy, birch, dog	Larger than negative control	IDST only compared with RAST; positive IDST result and positive RAST result, 86% agreement; NPV of IDST, 96%; 85% correlation among IDST, RAST, and provocation testing
Brusasco et al ⁴⁴	384	1,000-5,000 PNU	Diluted 100 times	6+ mixes	Not specified	Correlation: SPT/RAST, 82%; IDST/RAST, 68%; positive SPT result and positive BPT result, 54.5%, vs positive IDST results and positive BPT result, 42.8%
Escudero et al ⁴⁵	31 With AR, 34 with asthma	100 BU/mL	0.1 and 1 BU/mL	<i>Alternaria tenuis</i>	IDST: wheal $\geq$ 5 mm with or without erythema	Gold standard: positive history (rhinitis or asthma) plus positive challenge; Coni, SPT, and IDST all with better sensitivity and specificity than RAST; IDST performance characteristics: sensitivity (94.1–100%), specificity (92.0–92.3%), PPV (80–88.9%), NPV (95.8–100%)

Abbreviations: AR, allergic rhinitis; BPT, bronchoprovocation testing; BU, bioequivalent units; Coni, conjunctival challenge; DM, dust mite; IDST, intradermal skin test; NPV, negative predictive value; PNU, protein nitrogen units; PPV, positive predictive value; RAST, radioallergosorbent test; SBE, standardized biological units; SPT, skin prick test.

Table 6. Comparison of IDST and RAST^a

Study	No. of study participants	IDST (wt/vol)	Allergen	Positive criteria	Results
Tang and Wu ⁴⁷	198	1:500	Multiple	5- to 10-mm wheal	RAST compared with IDST as gold standard; good agreement with DM (95%), intermediate for Bermuda and ragweed (70%–73%), poor for dog and <i>Candida</i>
Norman et al ⁴⁸	87	Varying	Ragweed	2+	IDST compared with RAST and histamine release; 68/80 with positive IDST results had positive histamine release; 7/7 with negative IDST results had negative histamine release results; good IDST and RAST correlation
Rappaport et al ⁴⁹	81	Not specified	Multiple	8- to 12-mm wheal	Comparison of IDST to RAST, no challenges; IDST/RAST: 70%–77% concordance
Van der Zee et al ⁵⁰	660	1,000, 100, 10 SQ-U/mL	Grass, cat, DM	>5-mm wheal	Agreement for IDST/RAST, 94%, 93%, and 92% for grass, DM, cat, respectively; 85% (23/28) of patients with negative SPT and positive IDST results had positive histamine release results

Abbreviations: DM, dust mite; IDST, intradermal skin test; RAST, radioallergosorbent test; SPT, skin prick test; SQ-U/mL, ALK standard quality units.

^a SPT not routinely performed.

looked at total IgE, RAST, and IDST to 10 allergens in 198 asthmatic children. RAST was highly sensitive and efficient overall when compared with IDST; both were excellent for dust mite, intermediate for pollens (Bermuda, ragweed), and less favorable for dog and *Candida*. Norman et al⁴⁸ studied 87 patients and found that a routine IDST compared well with RAST and histamine release in ragweed hay fever. Rappaport et al⁴⁹ studied 81 children from an urban pediatric allergy clinic population, 51 untreated and 30 receiving immunotherapy. Overall, agreement between IDST and RAST was 77% for untreated patients and 70% for immunotherapy patients. A significant number of patients with negative SPT results and positive RAST results were found (more in the immunotherapy group). House dust had a significantly higher number of positive IDST results than RAST (57 vs 27%), whereas the opposite was true for ragweed (20 vs 57%). Thus, the performance among different allergens was markedly variable.

Van der Zee et al⁵⁰ studied discrepancies between ID and RAST for grass, dust mite, and cat by using histamine release assays, complement activation, and IgG4 levels. The percentage of agreement between IDST and RAST was 94%, 93%, and 92% for grass, dust mite, and cat, respectively. Most (84%) discordant results were positive IDST result and negative RAST result. Reproducibility of RAST and the IDST was evaluated in this discordant group. Additional RASTs were similar in 81%. The IDST was performed again on

remaining discordant results, and 89% of results were similar. Eighty percent of positive IDST results and negative RAST results were negative to all 3 in vitro systems. Eighty-five percent of patients tested from this group had a positive histamine release assay result to the relevant allergen. All positive histamine release test results were from patients who had positive SPT results at 100 ALK standard quality units (SQ-U/mL), whereas a positive SPT result at 1,000 SQ-U/mL did not lead to any positive histamine release test results. They believed that positive IDST results and negative RAST results were likely caused by very low IgE antibody titers that were undetectable by in vitro assays or by allergenic components only present in low concentrations in the extract. Therefore, the IDST and RAST compare well if you perform the IDST on all patients and not only on the SPT-negative patients. However, SPTs typically are superior, obviating the need for IDSTs in most instances.

CONCLUSION

The IDST is safe, is reproducible, and can quantify sensitivity. For inhalant allergy, a positive IDST result is associated with a positive in vitro test result in approximately 5% of SPT-negative patients with relevant histories and generally has low agreement with challenge results. Conversely, a negative IDST result may be helpful for ruling out IgE-mediated disease. The IDST adds little to the diagnostic evaluation of cat and timothy grass allergy yet may have a

role in the diagnosis of *Alternaria* hypersensitivity. For lower potency or nonstandardized allergens, the IDST may identify a higher percentage of patients with lower levels of clinical sensitivity and a positive test result may be more clinically relevant. Studies that use challenge models are needed for additional aeroallergens, particularly, dog, trees, weeds, and molds. Therefore, with a compatible history and a negative or equivocal SPT result, selective IDSTs may be indicated in these situations.

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Requests for reprints should be addressed to:
 Christopher W. Calabria, MD
 Wilford Hall Medical Center
 2200 Bergquist Dr, Suite 1
 Lackland AFB, TX 78236
 E-mail: christopher.calabria@lackland.af.mil

Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

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CME Examination

1–5, Calabria CW, Hagan L. 2008;101:337–347.

CME Test Questions

1. Most studies suggest that the proper dilution from the stock extract for intradermal skin testing (IDST) for inhalant allergy should be:
 - a. 10- to 100-fold
 - b. 100- to 1,000-fold
 - c. 10,000-fold
 - d. 100,000-fold
 - e. 1,000,000-fold
2. The intradermal histamine control should be:
 - a. 10-fold weaker than the prick histamine (0.1 mg/mL)
 - b. the same as the prick histamine control (1 mg/mL)
 - c. 100-fold weaker than the prick histamine control (0.01 mg/mL)
 - d. 1,000-fold weaker than the prick histamine control (0.001 mg/mL)
 - e. 10-fold stronger than the prick histamine (10 mg/mL)
3. Of patients with a negative skin prick test (SPT) result, what percentage with a positive IDST result have a positive in vitro test result?
 - a. 80%–90%
 - b. 90%–100%
 - c. 5%–10%
 - d. 50%–60%
 - e. 30%–40%
4. Several studies have been presented that use challenge models (cat, timothy, grass) to evaluate the diagnostic

performance of the IDST. In these studies, patients with a negative SPT result then received IDSTs. These studies have shown that:

- a. Patients with a positive IDST result are twice as likely to have a positive challenge result than those with a negative IDST result.
 - b. Patients with a positive IDST result are 4 times as likely to have a positive challenge result than those with a negative IDST result.
 - c. Patients with a negative IDST result are just as likely to have a positive challenge result as those with a positive IDST result (within 5%–10%).
 - d. A positive IDST result always predicts a positive challenge result.
 - e. Patients with a positive IDST result test are 10 times as likely to have a positive challenge result than those with a negative IDST result.
5. The volume of inhalant allergen that should be injected for IDST is:
 - a. 0.1–0.2 mL
 - b. 0.002–0.1 mL
 - c. 0.2–0.5 mL
 - d. 0.02–0.05 mL
 - e. 1–2 mL

Answers on page 418.