

Diagnostic evaluation of type I latex allergy

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Background: Latex hypersensitivity affects a significant number of health care workers. No universally accepted method for the diagnosis of latex allergy is currently available in the United States.

Objective: Determine the accuracy of clinical assessment in predicting type I latex allergy, and compare the ability of various latex skin test preparations and in vitro assays in confirming the diagnosis of latex allergy.

Methods: Subjects were classified into "history positive," "history ambiguous," or "history negative" based on reports of clinical symptoms. Skin prick tests were performed with ammoniated latex and glove extracts. Sera were analyzed for latex-specific IgE using the Pharmacia CAP and DPC AlaSTAT assays.

Results: A total of 207 subjects had histories taken, skin testing, and blood drawn. Out of 49 type I latex-allergy "history positive," 42 (86%) were skin test positive, and 24 (49%) were serum positive. Fifty-nine subjects were latex allergy "history ambiguous." In this group, skin testing showed 19 (32%) positives, and latex-specific IgE were detected in 10 (17%). Out of 99 latex "history negative," 9 (9%) were skin test positive, and 11 (11%) were positive for latex-specific IgE. Out of the 61 subjects with IgE symptoms following latex exposure who were skin test positive, a positive in vitro assay was found in 32 (52%).

Conclusions: Skin testing is more likely to confirm a positive latex allergy history. Use of raw ammoniated and glove skin testing preparation sources combined adds to the diagnostic sensitivity. AlaSTAT and CAP correlate well with each other and have good negative predictive value, but lack the sensitivity of skin testing. Use of AlaSTAT and CAP assays combined raises the diagnostic sensitivity as compared to using one in vitro test alone.

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INTRODUCTION

A clinical history of type I latex allergy especially, but not necessarily, when associated with risk factors like spina bifida or occupational exposure requires special attention.^{1–3} Type I hypersensitivity to hevea latex (also known as natural rubber latex) is the result of latex protein-specific IgE antibodies that are capable of inducing histamine release from sensitized mast cells and basophils.⁴ Patients who have this allergy experience symptoms of

IgE-mediated disease that vary from localized hand symptoms such as itching and urticaria, to a wide range of systemic symptoms including generalized urticaria, sneezing, tearing, cough, wheezing, hypotension, and shock.^{4–6}

The diagnosis of type I hypersensitivity to natural rubber latex is currently confirmed by in vivo skin testing with raw latex or glove extracts, or by commercially available in vitro assays that measure latex-specific IgE.⁷ A glove "use test" first described by Turjanmaa et al may be performed for cases when there is discrepancy between skin test results and clinical history or when in vitro studies are positive in otherwise asymptomatic subjects.⁸ Bronchial provocation testing with aerosolized latex has recently been described.^{4,9,10} Other research-based in vitro tests of latex allergy include ELISA, immunoblots, cellular

proliferation assays, basophil histamine release, and flow cytometry.^{11–16}

In this study we evaluated how clinical assessments based on patient histories compare with test results from ammoniated and glove latex prick skin testing preparations and two commercially available in vitro latex-specific IgE assays.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of Long Beach Memorial Hospital. Study population consisted of all patients (mostly health care workers) referred to our office for latex evaluation between February 1994 and December 1996. In addition, subjects were recruited during Long Beach Memorial's annual safety fairs in 1995 and 1996. All study subjects were required to sign a consent form detailing the study and potential risks prior to enrollment. Enrollment was contingent upon subject's approval to undergo both skin and blood testing.

Study Questionnaire

Patients were interviewed by study investigators and assigned an overall pre-testing clinical impression of being type I latex allergy "history positive," "history negative," or "history ambiguous," as shown in Table 1. "History positive" patients were defined as those consistently having urticaria, bronchospasm, anaphylaxis, or rhinoconjunctivitis less than one hour following latex exposure. Patients were given a "history ambiguous" labeling for having the above symptoms occur inconsistently, in the presence or absence of exposure to latex. A "history ambiguous" patient is defined as somebody with pre-existing asthma or allergic rhinitis with inconsistent worsening around latex, or a patient having delayed onset (more than 60 minutes) of IgE symptoms following latex exposure. "History negative" patients

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Table 1. Pre-Testing Clinical Classification of Study Participants

	Positive*	Ambiguous*	Negative*
IgE-mediated symptoms following latex exposure	Any or all of: rhinoconjunctivitis, urticaria, bronchospasm, anaphylaxis	Any or all of: rhinoconjunctivitis, urticaria, bronchospasm, anaphylaxis	None
Onset following latex exposure	Less than one hour, usually in minutes	More than one hour	N/A†
Frequency following latex exposure	Almost always	Occasional or intermittent	N/A†
Improvement with avoidance of latex	Almost always	Occasional or intermittent	N/A†
Irritant or contact dermatitis	Possible	Possible	Possible

* Classification was done prior to any skin or blood testing and refer to type I latex allergy.

† Not applicable.

were defined as those having no evidence of type I symptoms following latex exposure. Patients reporting irritant or contact dermatitis to latex exposure could be in any of the three groups as the presence of these symptoms had no bearing on their type I classification.

Skin Prick Test

Skin testing was performed on all consenting participants. Testing was done by the epicutaneous method on the forearm with two groups of latex testing materials. The first group consisted of three separate batches of unmodified raw ammoniated latex (two batches from Johnson and Johnson, New Brunswick, NJ, and one batch from ALK Laboratories, Wallingford, CT). The second skin testing group consisted of three latex glove extracts (DigitCare, Los Angeles, CA; Safeskin, Boca Raton, FL; and VHA-Ansell, Eatontown, NJ) prepared as previously described.¹⁷

IBT Reference Laboratories (Lenexa, KS) measured the latex allergen content using an ELISA inhibition assay developed from pooled latex-allergic patient sera. The milligram of allergen per milliliter of the skin prick extracts were (1) ammoniated batch #1 (Johnson & Johnson), 2.61, (2) ammoniated batch #2 (Johnson & Johnson), 3.64, (3) ammoniated batch #3, (ALK Laboratories), 2.22, (4) Digitcare glove extract, 2.49, (5) Safeskin glove extract, 2.55, and (6) VHA glove extract, 2.91.

Skin testing was done by the punch technique, using the DermaPIK (Greer Laboratories, Lenoir, NC) and read 15 minutes after application.¹⁸ Histamine phosphate 1 mg/mL was used as positive control, and albumin-saline solution as negative control (Hollister-Stier, Spokane, WA). Results were considered positive if the largest wheal diameter was 50% or greater than that of the histamine control, and at least 3

mm larger than the negative saline control.

A positive raw skin test was defined as a positive result to at least one of the three raw testing materials. Similarly, a positive glove skin test was defined as a positive result to at least one of the three glove prick test materials. The overall skin prick test was defined as positive if at least one of the raw or glove skin pricks was positive. Medications to treat adverse reactions were readily available.

Latex-Specific IgE

Blood was obtained by peripheral venipuncture from all consenting subjects. Serum was separated and analyzed for latex-specific IgE using two FDA (Food and Drug Administration, USA) approved assays, the CAP (Pharmacia Biotech, Uppsala, Sweden) and AlaSTAT (Diagnostic Products Corp, Los Angeles, CA) assays. Either test was defined as positive if the result was class I or higher. The overall blood test was defined as positive if one or both tests was(were) positive.

RESULTS

Study Questionnaire Results

A total of 207 patients had extensive histories, skin tests, and blood drawn. Based on clinical history and prior to any diagnostic testing, 49 (24%) patients were coded as "latex history positive," and 99 (48%) were coded as "latex history negative." Fifty-nine patients (29%) were labeled as "history ambiguous" due to inconsistent or delayed (more than one hour) IgE-related symptoms following latex exposure (Table 1). Rhinoconjunctivitis and urticaria (systemic or local) were the most commonly reported IgE-related symptoms, occurring in 76 (37%) and 39 (19%) of the 207 patients, respectively (Table 2). Asthmatic symptoms were less common (12%), however they were more likely to occur in the clinically "positive" group versus other clinical classifications ($P \leq .001$). There was no statistically significant difference between the "history positive" and "history ambiguous" groups with regard to rhinoconjunctivitis. Ur-

Table 2. Clinical Symptoms of Study Population Following Latex Exposure

	Clinical Diagnosis of Type I Latex Allergy		
	Positive (n = 49)	Ambiguous (n = 59)	Negative (n = 99)
IgE symptoms	49	59	0
Urticaria	24	15	0
Rhinoconjunctivitis	36	40	0
Asthma	22	2	0
Anaphylaxis	6	0	0
Contact dermatitis	24	30	40

ticaria was more commonly reported in the “history positive” group than in the “history ambiguous” group. Anaphylaxis was the least common IgE-mediated symptom, and although it always resulted in a “history positive” labeling, the number of patients with this symptom was too small to achieve statistical significance. Overall, contact dermatitis was the most common symptom reported by study participants (45%) and was reported with nearly equal frequency in all clinical groups.

Skin Prick Test Results

Out of the 49 patients coded latex “history positive,” 42 (86%) were skin test positive (Fig 1a) versus only 9 of 99 (9%) of those coded “history negative.” Latex skin test was positive in 19 of 59 (32%) “history ambiguous” patients. Ammoniated raw latex was more likely than glove-based preparations to yield a positive prick test result in all clinical groups, as shown in Figure 1a, with the ammoniated raw extract picking up 81.4% of the positive skin tests and glove extracts picking up 74.3%. There was no significant difference between the individual testing materials within each group of the latex preparations used in this study (data not shown). Adverse reactions to skin testing were limited to rhinoconjunctivitis in three subjects. All three patients were treated uneventfully with an oral antihistamine.

Latex-Specific IgE Results

Of the 49 “history positive” subjects, 22 (45%) were AlaSTAT positive (class I or higher), and 17 (35%) were CAP positive (Fig 1b). In the 59 “history ambiguous” group the AlaSTAT and CAP were positive in 8 (14%) and 6 (10%), respectively. Out of 99 patients coded “history negative,” 11 (11%) were positive for latex-specific serum IgE. Nine (9%) of these 99 were also skin test positive.

History and Skin Test Versus In-Vitro Assay Results

Out of the 61 subjects with IgE symptoms following latex exposure (“history positive” or “history ambiguous”)

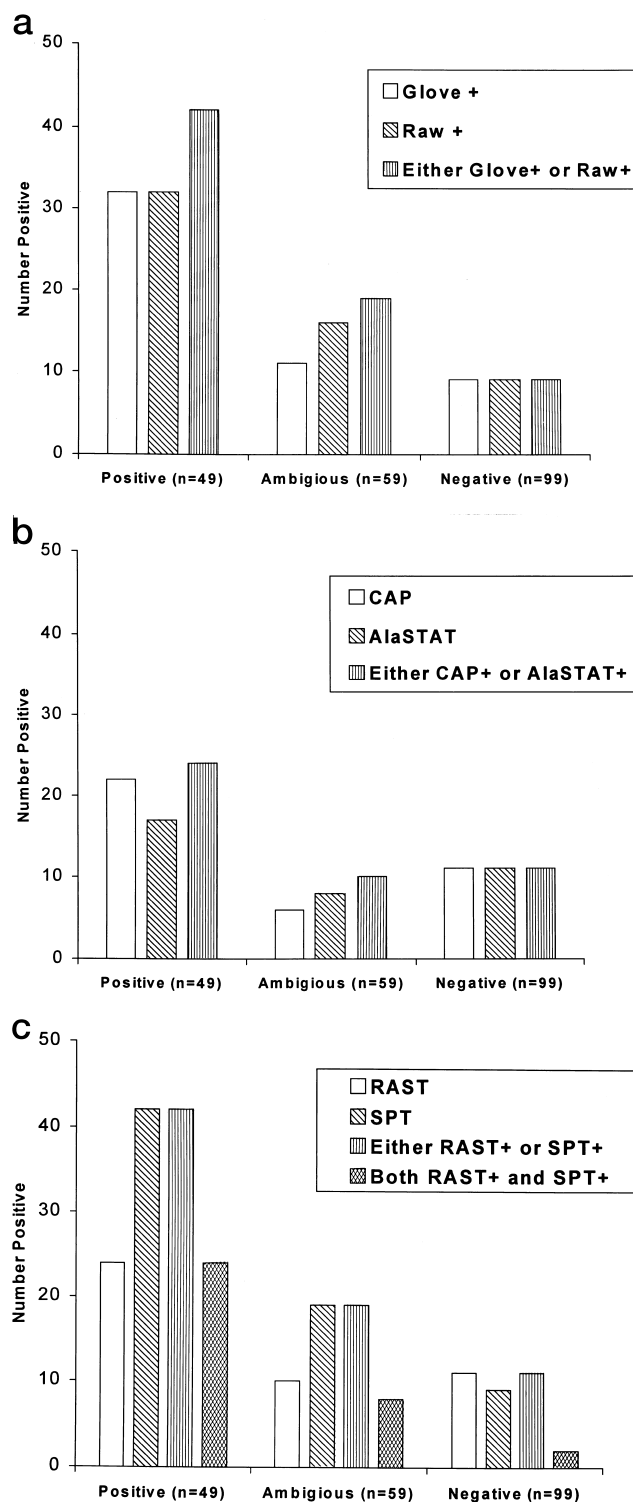


Figure 1. Latex skin prick and latex-specific serum IgE test results according to pretesting classification: (a) skin prick, (b) latex specific IgE, and (c) skin prick and latex specific serum IgE.

who were also skin test positive, a positive in vitro assay was found in 32 (52%), with AlaSTAT being positive in 23 (38%), and CAP being positive in 27 (44%) (Fig 1c). Out of 90 subjects who had no history of IgE symptoms following latex exposure ("history negative") and who were also negative on skin testing, both in vitro assays were negative in 82 or 91%. AlaSTAT and CAP were negative in 87 (97%) and 84 (93%), respectively.

DISCUSSION

Although a convincing history of IgE symptoms with latex exposure is a reliable indicator of latex allergy in most patients, symptoms such as those of rhinoconjunctivitis and asthma are commonly a result of other environmental allergies and can be a source of diagnostic bias. In a recent study by Hamilton et al,¹⁹ a careful clinical history incorrectly diagnosed latex allergy in 15% of the subjects. These patients had a very high clinical score indicative of latex allergy, but were completely negative on latex skin testing, serologic tests, and glove provocation tests. Similarly in this study, of the 49 with convincing history of IgE-mediated symptoms, seven patients (14%) were still negative to all latex skin tests, and to both the AlaSTAT and CAP assays (Fig 1a).

In contrast, lack of IgE-mediated symptoms in relation to latex was found in 99 subjects. Within this clinically "history negative" group, 9 subjects had a positive skin test and 11 had a positive in vitro assay (Fig 1c). Given that the in vitro tests did not

pick up any more positive cases than skin tests in the "history positive" and "history ambiguous" groups, it appears the increased number of positive in vitro tests in the "history negative" group are more likely to be false positives. Although a "false" positive skin test or in vitro assay with a negative history of IgE symptoms following latex exposure can be the result of cross-reactive IgE antibodies,^{20,21} it may also be an early indicator of latex allergy and as such these patients should avoid latex exposure.

Furthermore, the ability to classify patients based on their symptoms as allergic to latex or not allergic to latex is not always possible, as we identified a total of 59 patients, or 29% of the study population, who have inconclusive symptoms of IgE-mediated latex allergy. In this group, a positive result to skin testing was found in 19 patients (32%), a positive RAST was present in 10 (17%), and both testing methods were still positive in eight patients (Fig 1c).

As shown in other studies, our results confirm the relatively high degree of sensitivity and safety of either ammoniated or glove latex extracts.²²⁻²⁴ Using both ammoniated and glove latex extracts increases the sensitivity of the skin testing method. Although ammoniated extracts may be easier to standardize, these extracts might be omitting important neo-antigens that develop as a result of chemical modification by agents used in the manufacturing process.²⁵ The lack of a standardized skin testing material to latex to date in the United States and rare

reports of adverse reactions to latex skin testing material are the factors preventing widespread use of this method in clinical practice.

The challenge of making the diagnosis of latex allergy is that no gold standard has been universally accepted. When clinical history is taken to be the gold standard, in vitro RAST assays for latex-specific IgE lack the sensitivity of prick skin testing (Table 3). From another perspective, when prick skin testing is chosen as the gold standard, in vitro RAST assays are not as sensitive as the clinical history. Similar to our study, a recent abstract by Kadambi et al reported that prick skin tests appear more sensitive than the Johns Hopkins RAST and the AlaSTAT assay.²⁶ Another recent study by Beebe et al, where history was the presumed gold standard, has found similar lack of sensitivity of a RAST assay, with just 12 of 88 (14%) history positive subjects being RAST positive.²⁷ Predictive values for any assay will depend upon what gold standard is used to define a type I latex-allergic patient.

CONCLUSION

The use of clinical assessment in combination with skin testing and commercially available RAST assays provide the current basis in making the diagnosis of latex allergy (Table 3). Clinical history alone is inadequate in establishing the diagnosis of type I latex allergy. Although skin prick testing is a sensitive method of confirming a clinically significant history of latex allergy, there is a present lack of a standardized reagent in the United States. The two FDA-approved in vitro latex-specific IgE assays suffer from a relatively low sensitivity if compared with prick skin testing. Using both assays (CAP and AlaSTAT) together, however, adds to their diagnostic sensitivity (Fig 1b).

In the clinical setting, patients with discordant clinical history, skin test results, and/or serologic tests pose a diagnostic dilemma. Under these circumstances, availability of a standardized challenge procedure such as a la-

Table 3. Comparison of Diagnostic Ability of Clinical History, Skin Test, and in Vitro Latex IgE Assays

"Gold Standard"	Sensitivity	Specificity	PV+*	PV-*
Clinical history†				
Overall skin test	86%	91%	82%	93%
Overall blood test	49%	90%	71%	78%
Overall skin test				
Clinical history†	82%	93%	86%	91%
Overall blood test	49%	93%	77%	78%

* PV+ = positive predictive value and PV- = negative predictive value.

† Patients with either "history positive" or "history negative" labeling, but not including those who are "history ambiguous."

tex glove use test and/or a bronchial provocation with aerosolized latex can be particularly useful.^{9,19} Challenge testing would be useful for a patient who has a convincing history of type I latex allergy but who is otherwise negative by both skin testing and in vitro assays. A negative challenge test under these circumstances makes it highly unlikely that this patient has true type I latex hypersensitivity.⁹

Similarly, challenge procedures can be used in patients who are asymptomatic but have a positive latex skin prick test or a positive in vitro assay to distinguish between those with false-positive tests from those who are truly latex allergic but are not yet symptomatic. When provocation testing is not done, these patients should be managed as if they were latex allergic since their next latex exposure could result in a life-threatening reaction.²⁸ In the future a standardized challenge procedure should help establish a gold standard definition of a type I latex-allergic patient.

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