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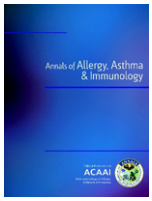

Analysis of available diagnostic tests for latex sensitization in an at-risk population

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ABSTRACT

Background: Lack of a Food and Drug Administration (FDA)–approved skin testing reagent for latex allergy in the United States requires reliance on patient history and serologic assays for diagnosis.
Objective: To determine the diagnostic sensitivity, specificity, and predictive values of an FDA-cleared antilatex IgE serology test and an enzyme-linked immunosorbent assay (ELISA) with various sources of latex protein antigens in an at-risk but unselected population of health care workers.
Methods: Health care workers underwent duplicate latex and serologic testing for latex specific IgE with the CAP assay and ELISA from June 1, 1998, through December 31, 2002. Logistic regression with receiver operating characteristic curve analysis determined the values, resulting in 98% and 99% specificity for the CAP assay and ELISA, respectively.
Results: Results of paired skin and serologic tests were available for 792 participants. Forty duplicate skin test results (5%) were positive. For the CAP assay, sensitivity was 35%; specificity, 98%; positive predictive value, 48.3%; and negative predictive value, 96.6%. ELISA demonstrated similar results. Multivariable logistic regression yielding a 98% or 99% specificity for the various ELISAs demonstrated that the adjusted odds of a positive skin test result significantly increased with positive CAP assay and ELISA results using a powdered glove extract.
Conclusions: The performance of the FDA-cleared antilatex IgE serologic test for latex allergy has much lower sensitivity than previously reported. This finding confirms that this serologic test should be used only for patients with a history of latex allergy and not for screening the population with a low prevalence of latex sensitization.

Introduction

Diagnosis of natural rubber latex allergy is important for both a patient's future medical care and working conditions of health care workers[1,2] (including worker compensation claims[3]). Suspicion of latex allergy begins with the history of exposures and reactions to latex, and confirmation is achieved through various testing methods. A comprehensive history will ascertain the likelihood of an immediate hypersensitivity to natural rubber latex and support the need for confirmatory testing. However, history alone can lead to up to a 15% false-positive rate of diagnosis of latex allergy[4,5]; therefore, reliable confirmatory testing for latex allergy is needed.

The confirmatory test of choice for most IgE-mediated allergies is the skin test with standardized allergen solutions. In the 1990s, a standardized latex allergen solution was developed by Greer Pharmaceuticals (Lenoir, North Carolina). This solution was used in multiple clinical investigations of latex allergy and was found to have a diagnostic sensitivity of 95% and specificity of 99% at a concentration of 100 μg/mL of purified latex antigen.[4,5] However, no standardized extract has been approved by the Food and Drug Administration (FDA) for clinical use.

Because there is no approved extract for skin testing of latex allergy, physicians must rely on other confirmatory tests, which include serologic testing to identify latex specific IgE.[3,6] There are currently 3 FDA-cleared assays for detecting latex specific IgE[6] and 1 clinically offered but non–FDA-cleared enzyme-linked immunosorbent assay (ELISA).[7,8] The diagnostic performance of the 3 FDA-cleared assays was assessed by the Multicenter Latex Skin Testing Task Force in the 1990s in a study with a prevalence of just

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more than 40% latex sensitization.[9] Two of the assays, the Pharmacia CAP-FEIA radioallergosorbent test (Pharmacia, Baltimore, Maryland) and the AlaSTAT Microplate assay (Diagnostic Products Corporation, Los Angeles, California), performed similarly, with a sensitivity of 76.3% and 73.3% and a specificity of 96.7% and 97.2%, respectively. The third assay, the HY-TEC EIA system (HYCOR Biomedical, Irvine, California), was significantly different, with a diagnostic sensitivity of 91.6% and specificity of 73.3%.[9,10] There are currently no published reports on the sensitivity and specificity of the ELISA test for antilatex IgE.

Serologic tests for latex allergy have been evaluated to determine whether they could be used as screening tests for latex allergy in the general population.[11,12] However, these studies noted high rates of positive serologic test results without evidence of clinically relevant latex allergy. To improve our understanding of the clinically available testing mechanisms for latex allergy, we investigated the diagnostic performance of available serologic assays for latex allergy. Unlike previous studies of antilatex IgE assays,[9,10] this study reports on an unselected but at-risk population of workers exposed to latex. The prevalence of latex allergy in this population more closely approximated the prevalence in at-risk groups and, therefore, will give more meaningful insight into the diagnostic performance of latex allergy testing.

All patients gave informed consent approved by the institutional review boards of the hospital, medical school, FDA, and Centers for Disease Control and Prevention of the National Institute of Occupational Safety and Health. In addition, the authors have no conflict of interest with any of the makers of the cleared FDA-approved assays or Greer Pharmaceuticals. The ELISA test is performed in the allergy/immunology laboratories of the Medical College of Wisconsin.

Methods

The study was performed from June 1, 1998, through December 31, 2002, and was approved by the institutional review boards at Children's Hospital of Wisconsin, Froedtert Memorial Lutheran Hospital, the Medical College of Wisconsin, the FDA, and the Human Subjects Review Board at the Centers for Disease Control and Prevention of the National Institute for Occupational Safety and Health. Data were collected after written informed consent was obtained in a study on latex sensitization in health care workers before and after a change in glove use at their workplace.[13] At each yearly visit, participants underwent skin prick tests (SPTs) with Clone 600 nonammoniated latex (IND 4920; Greer Pharmaceuticals). Testing was performed by the same technician at each visit. SPTs were performed in duplicate (2 simultaneous latex SPTs) with serial dilutions of the latex serum as described previously.[5] A positive test result at any dilution point was considered diagnostic of latex sensitization. Serologic testing was also performed at each visit and consisted of the CAP assay (with antigen k82) and ELISA for latex specific IgE. The CAP assay was performed per the manufacturer's guidelines as described previously.[9] ELISA was performed using 4 different latex antigen preparations: Clone 600 nonammoniated latex (Greer Pharmaceuticals), Malaysian nonammoniated latex (tree sap), and preparations from extracts of 2 commercially available latex powdered gloves. The assay was performed with patient serum in a dilution of 1:10 in the manner described previously.[7] This study used data from the first year of testing only.

The sensitivity and specificity of the CAP assay were calculated using previously published cutoff values (>0.35 kUA/L) and the data from paired skin test and serologic tests. Logistic regression analysis was used to create receiver operating characteristic (ROC)

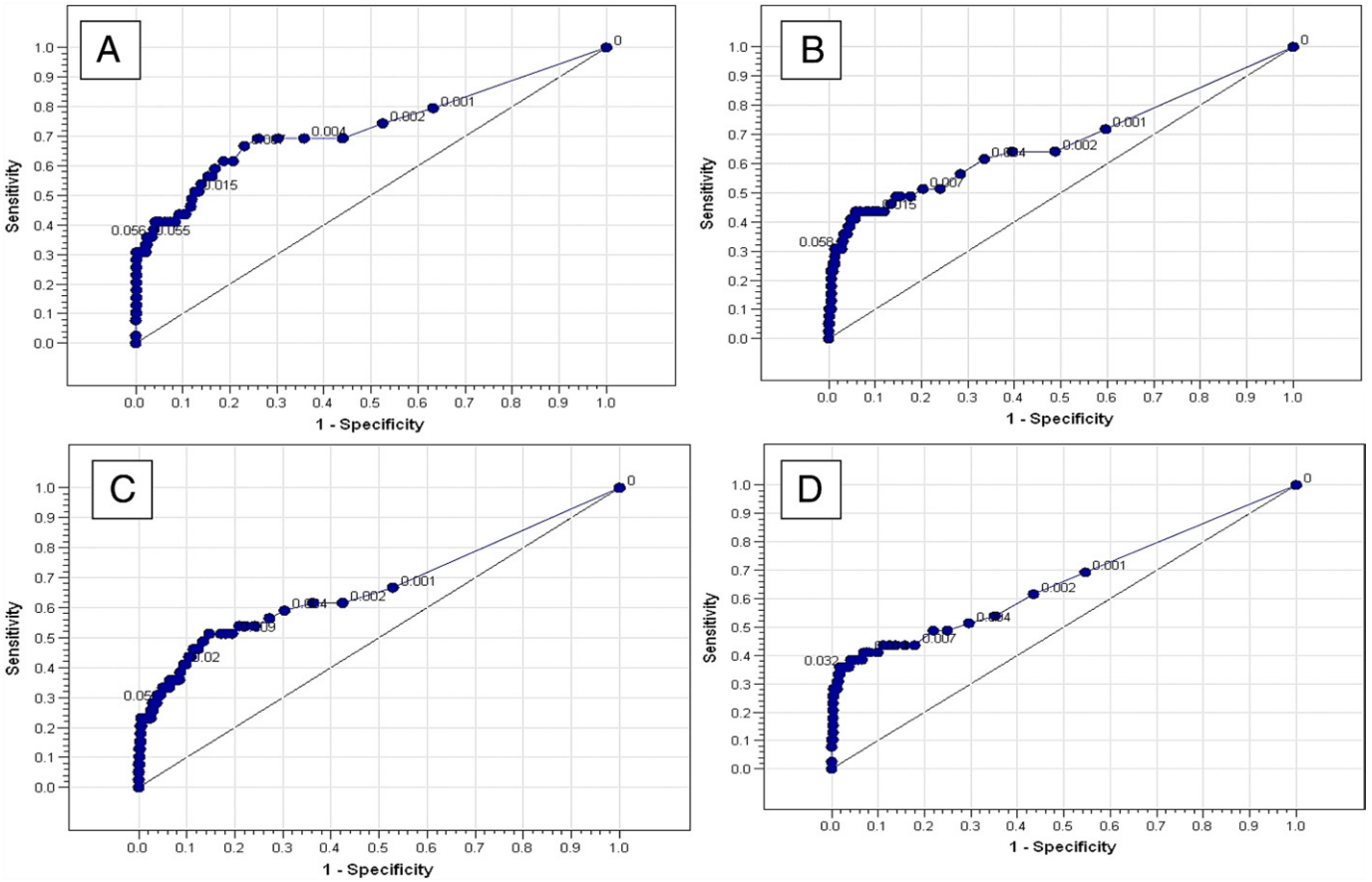

Figure 1. Receiver operating characteristic curves for 4 latex specific IgE antibody enzyme-linked immunosorbent assays. **(A)** Clone 600 antigen (area under the curve [AUC] = 0.755). **(B)** Latex glove 1 antigen (AUC = 0.683). **(C)** Malaysian nonammoniated antigen(AUC = 0.672). **(D)** Latex glove 2 antigen (AUC = 0.663).

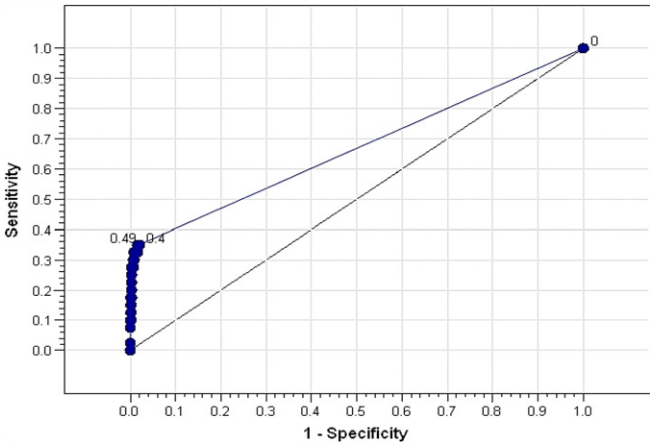

Figure 2. Receiver operating characteristic curve for the CAP assay for latex specific IgE antibody (area under the curve = 0.667).

curves for each of the 4 ELISAs. Data from this analysis were used to determine the cutoff values for the 4 ELISAs, which gave a diagnostic sensitivity of 98% and 99%. Positive and negative predictive values of each of the tests were calculated.

Multivariable logistic regression was performed to identify whether using more than 1 of the available serologic tests significantly increased the odds of correctly identifying patients with a positive SPT result. For this analysis, the values for the serologic tests were transformed into categorical variables (ie, positive or negative test result) using the cutoff values identified in the creation of the ROC curves. All analyses were performed with SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina), and statistical significance was defined as $P \leq .05$.

Results

Results of paired skin testing and all 4 serologic tests were available for 792 participants. There were 40 positive SPT results in the first year of the study, yielding a prevalence of latex sensitization of 5% in this high-risk population. Of 39 patients with positive SPT and CAP assay results available, only 17 had both positive SPT and CAP assay results (false-negative rate of CAP assay, 67%).

ROC curves were created for all of the serologic assays. The area under the curves for the ELISAs ranged from 0.663 to 0.755 (Figure 1). The area under the curve for the CAP assay was 0.667 (Figure 2). The values giving a diagnostic sensitivity of 98% and 99% for latex sensitization for each assay were determined. Latex specific IgE CAP testing had a 98% specificity at 0.35 kUA/L (the manufacturer's recommended cutoff value) and a sensitivity of 35.9% (Table 1). To achieve a diagnostic specificity of 99% with the CAP assay, the cutoff value must be raised to 0.64 kUA/L, which causes a decrease in sensitivity of 32.5% (Table 2). The ELISAs similarly showed low sensitivities at cutoff values, yielding a specificity of 98% (Table 1) and 99% (Table 2). However, 2 of the assays (ELISA with Clone 600 and with Malaysian nonammoniated antigen) did not show a change in the sensitivities when the cutoff value was changed to a level with a specificity of 99%.

Multivariable logistic regression was performed with categorical variables for the serologic tests at cutoff values yielding 98% and 99% specificity to identify whether a combination of tests increased the odds of identifying patients with latex sensitization. Using the cutoff values yielding 98% specificity, positive test results for both the CAP assay and ELISA with glove extract 1 were significantly associated with latex sensitization (Table 3). However, when the 99% specificity cutoff values were used, only a positive CAP assay result was significantly associated with latex sensitization (Table 3).

Table 1
Cutoff values, sensitivity, and predictive values to yield 98% specificity for assays

Test and antigen	Cutoff value for diagnostic specificity of 98%	Corresponding sensitivity, %	PPV,[a] %	NPV.[a] %
ELISA				
Clone 600	0.065	30.8	44.4	96.5
MNA (tree sap)	0.089	23.1	37.5	96.1
Glove 1	0.050	30.8	48.3	96.7
Glove 2	0.031	35.9	44.4	96.5
CAP	0.35	35	48.3	96.6

Abbreviations: ELISA, enzyme-linked immunosorbent assay; MNA, Malaysian nonammoniated; NPV, negative predictive value; PPV, positive predictive value.
[a]Predictive values are only valid for the prevalence of latex sensitization in this population.

Table 2
Cutoff values, sensitivity, and predictive values to yield 99% specificity for assays

Test and antigen	Cutoff value for diagnostic specificity of 99%	Corresponding sensitivity, %	PPV,[a] %	NPV,[a] %
ELISA				
Clone 600	0.149	30.8	63.2	96.5
MNA (tree sap)	0.128	23.1	56.3	96.1
Glove 1	0.091	25.6	61.1	96.4
Glove 2	0.048	28.2	58.8	96.3
CAP	0.64	32.5	68.4	96.5

Abbreviations: ELISA, enzyme-linked immunosorbent assay; MNA, Malaysian nonammoniated; NPV, negative predictive value; PPV, positive predictive value.
[a]Predictive values are only valid for the prevalence of latex sensitization in this population.

Discussion

Our study population demonstrated a prevalence of latex sensitization of 5%.[13] This prevalence is similar to the prevalence found in other at-risk populations at the time of this study[14,15] when occupational exposure to latex was high.

Our data demonstrate a significantly lower sensitivity of the FDA-cleared CAP assay than what was reported previously[9] and similarly low sensitivities for the experimentally available ELISAs. Therefore, among people who are truly sensitized to latex (as demonstrated by positive SPT results), there will be high rates of false-negative serologic tests for latex sensitization (false-negative rate of 67%), which will lead to misclassifying patients with latex sensitization as having negative results in 2 of 3 tests when the skin test result would have been positive. These data demonstrate that these serologic tests should never be used as screening tests in a population with a low prevalence of latex allergy.

Table 3
Multivariable logistic regression analysis using categorical values (Positive or negative at 98% and 99% specificity cutoffs) for serologic assays

Independent variable	Odds ratio for presence of latex sensitization (95% CI)	*P* value
CAP positive (>0.35 kUA/L, 98% specificity)	11.78 (4.24–32.68)	<.001
Glove 1 positive (at 98% specificity cutoff value)	6.58 (2.14–20.23)	<.001
CAP positive (>0.35 kUA/L, 99% specificity)	62.16 (21.90–176.44)	<.001

Abbreviation: CI, confidence interval.

Predictive values, unlike sensitivity and specificity, are related to the prevalence of the condition in the population being tested. In a population, such as this, with a low prevalence of latex sensitization, these examinations demonstrate high negative predictive values and low positive predictive values. In clinical practice, however, these tests are not used for screening the general population for latex sensitization (low prevalence). They are used to confirm or refute latex sensitization in persons in whom it is highly suspected based on the history (a higher prevalence population but where one can expect a 15% false-positive rate of latex sensitization diagnosis from history alone[4,5]). In a high prevalence population, the CAP assay will have a high positive predictive value, whereas the negative predictive value of the assay will be low. In this case, negative examination findings will be difficult to interpret; therefore, it will be difficult to rule out latex sensitization in the clinical context using the available serologic tests.[16, 17] Although it is possible for the physician to use the HY-TEC FDA-cleared test that historically had a higher sensitivity but many false-positive results, this new information may not be extrapolated to the performance of this test without direct comparison.

The use of multiple serologic tests for latex sensitization may be helpful in identifying latex sensitized patients as demonstrated by the multivariable logistic regression analysis. However, a highly positive CAP result (>0.64 kUA/L, 99% specificity) alone is also significantly associated with latex sensitization demonstrating that when the CAP assay result is strongly positive; further serologic testing may not be needed to delineate latex sensitization.

Limitations of this study are that glove challenge was not performed to confirm latex sensitization and patient history of reaction did not factor into our designation of latex sensitization. Although the SPT with Clone 600 antigen has very high sensitivities and specificities (95% and 99%, respectively),[4,5] it is not a perfect test. There may have been few false-positive and false-negative results from SPTs. A previous study[9] that used glove challenge to confirm SPT results when the results of testing were inconsistent with patient history found that 6 of 324 people needed to be reclassified (1 with a positive SPT result reclassified as negative and 5 with positive SPT results reclassified as negative). However, in a population with such a low prevalence of latex allergy, the few misclassified cases may have significantly altered the results.

This study of latex sensitization in an unselected but at-risk population demonstrated that the available serologic assays for determining latex sensitization are inadequate. In the diagnosis of an allergy that has significant ramifications on patients' future employment and health care, we must feel confident in our available testing. With the FDA-cleared and experimentally available testing that is currently available at this time, there is little that we can offer to patients whose history suggests a possible latex allergy but whose serologic testing is equivocal. Because of the uncertainty associated with the testing, we may be encouraging patients to avoid latex when that is not necessary. In addition, when the history is highly suggestive of allergy and the test result is negative, we may feel uncomfortable allowing future exposure for fear that the test result was false negative. This study demonstrates the need for an improved method of diagnosing latex allergy. Because of this, we support reevaluation of the safety and diagnostic utility of the Clone 600 SPT by the FDA for use in patients who are suspected of having latex allergy.

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