

Latex-specific IgE, skin testing, and lymphocyte transformation to latex in latex allergy

Didier G. Ebo, MD, Wim J. Stevens, MD, PhD, Chris H. Bridts, MT, and
Luc S. De Clerck, MD, PhD *Antwerp, Belgium*

Background: This study was designed to determine the discriminative value of latex-specific IgE tests, latex skin tests, and lymphocyte transformation tests (LTTs) to latex in 38 patients with latex allergy (12 nonatopic and 26 atopic) and 44 control subjects (24 nonatopic and 20 atopic). We also evaluated the recommended positive cutoff (i.e., 0.35 kU/L) of both in vitro latex-IgE tests.

Methods: Latex-specific IgE levels were determined by the Immuno-CAP (Upjohn-Pharmacia) and the ALaSTAT-RIA (Diagnostic Products Corp.) assays. Skin tests and LTTs were performed with a nonammoniated latex extract (DPC). Sensitivities and specificities were defined according to the 95th percentile value of nonatopic control subjects. For the in vitro IgE tests, sensitivity and specificity were also calculated by using the proposed positive threshold of 0.35 kU/L. Sensitivities and specificities of both cutoffs were compared. **Results:** Compared with a clinical history of latex allergy and according to the 95th percentile value of nonatopic control subjects (0.44 kU/L), latex-specific IgE determined by the Immuno-CAP assay achieved a sensitivity of 97% and a specificity of 86%. For the ALaSTAT-RIA assay, with 0.54 kU/L as the 95th percentile threshold value in nonatopic control subjects, sensitivity was 100%, and specificity was 83%. According to the threshold value of 0.35 kU/L, a sensitivity of 97% and a specificity of 83% for the Immuno-CAP assay and a sensitivity of 100% and a specificity of 33% for the ALaSTAT-RIA assay were observed. The latex skin test reached a sensitivity of 97% and a specificity of 100%. The LTT to latex showed a sensitivity of 39% and a specificity of 95%. No relation between symptoms and latex-specific IgE tests, latex skin tests, or LTTs was found. **Conclusions:** Our results confirm that latex skin tests and latex-specific IgE assessments are sensitive and specific methods for establishing the diagnosis of latex allergy, although the specificity of the ALaSTAT-RIA assay was very low when interpreted according to the threshold of 0.35 kU/L. The LTT to nonammoniated latex is too insensitive for diagnosis of allergy to latex. This reemphasizes that in order to evaluate the sensitivity and specificity of diagnostic procedures, one should always include an appropriate control group. (*J Allergy Clin Immunol* 1997;100:618-23.)

Key words: IgE, latex, lymphocyte proliferation, skin test

Natural rubber is cis-1,4 polyisoprene extracted from the milky sap, or latex, of the rubber tree *Hevea brasili-*

Abbreviations used

cpm:	Counts per minute
LTT:	Lymphocyte transformation test
NAL:	Nonammoniated latex
SI:	Stimulation index
SPT:	Skin prick test

ensis. Latex is composed of droplets of polyisoprene surrounded by a thin phospholipoprotein coat. Immediate hypersensitivity to latex was first reported in Germany in 1927.^{1,2} Only since 1989 has an IgE-mediated hypersensitivity to the constituent proteins in latex products been increasingly reported and reviewed.³⁻⁵ Diagnosis of latex allergy is made on the basis of a history suggesting a latex-induced reaction and the demonstration of an IgE-mediated reaction by positive skin test responses, the presence of specific IgE serum antibodies, or both. In the absence of standardized skin test reagents and because of the possible risks for anaphylaxis from skin testing,⁶⁻⁹ quantification of serum latex-specific IgE has been proposed as the initial step to establish the diagnosis of latex allergy.⁹⁻¹² Unfortunately, several serologic assays were reported to be inadequately sensitive.¹³⁻¹⁵ We evaluated the discriminative value of two commonly used latex-specific IgE determinations, the latex skin test and the lymphocyte transformation test (LTT) to latex, in patients with latex allergy and in control subjects. In addition, we compared the sensitivities and specificities of different cutoffs (i.e., the proposed threshold of 0.35 kU/L and the 95th percentile value of nonatopic control subjects) for the in vitro IgE tests.

METHODS

Study population

Eighty-two subjects (19 men and 63 women; age range, 14 to 60 years) were included in the study. Diagnosis of atopy was based on a history of childhood eczema, allergic rhinitis, conjunctivitis, or asthma, confirmed by serum-specific IgE levels and skin tests with common inhalant allergens. Patients were selected if they were first seen with a compelling history of latex allergy on the basis of the type of latex hypersensitivity (e.g., contact urticaria, rhinitis, conjunctivitis, angioedema, bronchospasm, generalized anaphylaxis with hypotension, or shock); job status; glove wearing; number of surgical and obstetrical procedures; and frequency of urogenital, rectal, or both types of manipulations with latex devices (e.g., catheterizations, condoms).^{4, 10, 12}

From the Department of Immunology, Allergy, and Rheumatology, University of Antwerp (UIA), Antwerp.

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Reprint requests: W. Stevens, MD, PhD, Department of Immunology, Allergy and Rheumatology, University of Antwerp, Universiteitsplein 1, B 2610 Antwerp, Belgium.

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The subjects were divided into four groups according to the presence or absence of atopy and a history of latex allergy. Group I consisted of nonatopic control subjects ($n = 24$; 8 men, 16 women; age, 18 to 60 years) without latex allergy. Atopy was ruled out by the absence of a history suggestive of atopic disease (e.g., asthma, rhinitis, atopic dermatitis), negative serum-specific IgE levels, and skin prick tests (SPTs) with the inhalant allergens. Group II consisted of atopic control subjects ($n = 20$; 8 men and 12 women; age range, 19 to 58 years) without latex allergy. Atopy was confirmed by a positive history corroborated by at least one positive SPT response, confirmed by a positive specific IgE level. Group III consisted of nonatopic patients with latex allergy ($n = 12$; 1 man and 11 women; age range, 25 to 55 years). Latex allergy was identified by a history of an immediate allergic reaction caused by latex exposure. Group IV consisted of atopic patients with latex allergy ($n = 26$; 2 men and 24 women; age range, 14 to 46 years). Atopy and latex allergy were confirmed as stated above.

Specific IgE

Quantification of serum-specific IgE for *Dermatophagoides pteronyssinus*, cat epithelium, *Alternaria tenuis*, *Cladosporium herbarum*, *Phleum pratense*, *Artemisia vulgaris*, *Betula verrucosa*, ethylene-oxide, and *Hevea* latex was performed with the Immuno-CAP assay (Upjohn-Pharmacia CAP System, Brussels, Belgium). Because of insufficient serum quantity, only 30 of 38 patient and 36 of 44 control serum samples could be assayed for latex-specific IgE in the ALaSTAT-RIA assay (Diagnostic Products Corp., Brussels, Belgium). Assays were performed according to the manufacturer's instructions. Briefly, for the CAP assay, latex antigens covalently bound to a cellulose matrix were incubated with patients' serum. After nonbound antibodies were washed, IgE was detected with mouse monoclonal I¹²⁵-labeled anti-IgE, and samples were counted in a gamma counter. Variation coefficients were between 7% and 14%. For the ALaSTAT-RIA assay, ligand-labeled latex and serum samples were incubated in ligand-coated tubes. Anti-ligand was added, and IgE-latex complexes were immobilized in the coated tubes. Unbound antibodies were removed by washing, and IgE was detected with mouse monoclonal I¹²⁵-labeled anti-IgE. Samples and standards were counted in a gamma counter. Variation coefficients were below 15%. Results were expressed quantitatively as international kilounits per liter. Sensitivities and specificities were calculated according to the 95th percentile value of nonatopic control subjects and according to the suggested cutoff of 0.35 kU/L. Inhibition experiments with serial dilutions of nonammoniated latex (NAL), starting at 0 μ g/ml and ranging up to 100 μ g/ml, were performed to evaluate the specificity of the assays.

Skin tests

SPTs were done with *Dermatophagoides pteronyssinus*, cat epithelium, *Alternaria tenuis*, *Cladosporium herbarum*, *Phleum pratense*, *Artemisia vulgaris*, and *Betula verrucosa* extracts (Haarlem Allergen Laboratories, Haadem, The Netherlands). For latex skin testing, nonammoniated latex (Diagnostic Products Corp.) was used. Skin prick and intradermal test titrations were performed with informed consent (SPT: 10^{-3} ranging up to 1 μ g/ml; intradermal test: 10^{-6} ranging up to 10^{-3} μ g/ml). The intradermal test was only performed in subjects with a negative SPT response at 1 μ g/ml. Because all control subjects had a complete negative skin test response up to the intradermal end-point concentration, skin tests responses were considered positive when the wheal reaction exceeded a diameter of 3 mm.

Latex LTT

Mononuclear cells were isolated from peripheral blood by Nycoprep (Nycomed, Oslo, Norway) density gradient centrifugation (density, 1.077 gm/ml). One hundred thousand peripheral blood mononuclear cells were cultured in 96-well round-bottom microtiter plates (Costar, Cambridge, Mass.) in 150 μ l of serum-free AIM-V medium (Life Technologies, Gent, Belgium) and stimulated with 20 μ l of NAL (10 μ g/ml) or medium as a negative control. The concentration of antigen used in this study was determined by preliminary experiments. The plates were incubated at 37°C in a humidified 5% CO₂ incubator (Jouan, Saint Herblain, France). After 6 days of culture, cells were pulsed for the final 24 hours with 20 μ l of methyl-tritiated thymidine (20 μ Ci/well; specific activity, 25 Ci/mmol) (Amersham Life Sciences, Amersham, U.K.). The cells were harvested with an automatic cell harvester (Filtermate 186; Canberra Packard Instruments, Medden, Conn.) on glass fiber paper (GF/C-Unifilter; Canberra Packard Instruments). The incorporated radioactivity was measured with a liquid scintillation counter (Topcount; Canberra Packard Instruments). Results were expressed as stimulation indexes (SIs) (i.e., counts per minute [cpm] of the latex-stimulated lymphocytes divided by cpm of the lymphocytes cultured with AIM-V medium). An individual SI exceeding the 95th percentile SI value of the nonatopic control subjects (4.80) was considered positive.

Statistical analysis

Results were expressed as median (range). The Mann-Whitney U test and Spearman's rank correlation test were applied where appropriate. Chi-square analysis was used to compare frequencies. Differences were considered significant at a p value less than 0.05.

RESULTS

Questionnaire data

Twenty-seven of the 38 patients, especially health care workers who routinely wore powdered latex gloves, reported occupational latex exposure. In eight of the remaining 11 patients, no clear risk factor was identified. Patients were first seen with local or generalized urticaria (25 of 38), rhinitis (11 of 38), conjunctivitis (16 of 38), and angioedema (25 of 38). Bronchospasm was observed in 12 patients. None had had generalized life-threatening anaphylaxis.

Specific IgE

The values of total serum IgE are presented in Table I. The values of latex-specific IgE are presented in Fig. 1, A and B. The number of positive results of latex-specific IgE are summarized in Table II. Latex-specific IgE detected by the Immuno-CAP assay, according to the 95th percentile of nonatopic control subjects (0.44 kU/L), was positive in 37 of 38 patients. Six (five atopic, one nonatopic) control subjects had a positive latex-specific IgE between 0.52 and 6.90 kU/L. When the threshold of 0.35 kU/L was used, the test responses were positive in 37 of 38 patients and in 7 of 44 control subjects (five atopic, two nonatopic). Latex-specific IgE detected by the ALaSTAT-RIA method, according to the 95th percentile of 0.54 kU/L in nonatopic control subjects, was positive in all patients and in 6 of 36 (five atopic, one nonatopic) control subjects, with a latex-specific IgE

TABLE I. Characteristics of patients

Sex	Age (yr)	Risk factor	Symptoms	Total IgE (kU/L)
Nonatopic patients (<i>n</i> = 12)				
F	39	HCW	Angioedema, urticaria	330
F	33	HCW	Bronchospasm, conjunctivitis, rhinitis, vaginal irritation	4
F	25	HCW	Bronchospasm, rhinitis, urticaria	150
F	44	HCW	Angioedema, urticaria	102
F	35	HCW	Rhinitis, urticaria	92
F	38	HCW	Angioedema, conjunctivitis, urticaria, vaginal irritation	70
F	37	HCW	Angioedema, conjunctivitis, rhinitis, urticaria	23
F	36	None	Angioedema, bronchospasm, urticaria, vaginal irritation	35
F	44	HCW	Angioedema, conjunctivitis, vaginal irritation	260
M	55	None	Angioedema, urticaria	710
F	34	HCW	Conjunctivitis, rhinitis, urticaria	120
F	29	HCW	Angioedema, bronchospasm, conjunctivitis, rhinitis	17
Atopic patients (<i>n</i> = 26)				
F	38	HCW	Angioedema, bronchospasm, conjunctivitis	36
M	35	HCW	Angioedema, urticaria	684
F	32	HCW	Angioedema, bronchospasm, conjunctivitis, urticaria	220
F	26	HCW	Urticaria	271
F	27	HCW	Conjunctivitis, rhinitis, urticaria	25
F	30	Industry	Urticaria	120
F	32	HCW	Angioedema	160
F	32	HCW	Angioedema, bronchospasm, conjunctivitis	190
F	28	HCW	Urticaria	584
F	46	HCW	Rhinitis	690
F	44	None	Angioedema, bronchospasm	2000
F	48	HCW	Urticaria	160
F	32	HCW	Angioedema, urticaria	2000
F	37	HCW	Angioedema, bronchospasm, conjunctivitis	290
F	38	HCW	Angioedema, conjunctivitis	320
F	32	None	Angioedema, urticaria	180
M	14	Surgery	Angioedema, bronchospasm, urticaria	860
F	29	Surgery	Angioedema	160
F	35	None	Bronchospasm, conjunctivitis, urticaria	88
F	34	HCW	Angioedema, rhinitis	220
F	34	HCW	Angioedema, conjunctivitis, rhinitis, urticaria	120
F	34	None	Angioedema, conjunctivitis, urticaria	110
F	27	None	Rhinitis	150
F	43	HCW	Angioedema, conjunctivitis, rhinitis, urticaria	67
F	24	None	Angioedema, bronchospasm, urticaria	270
F	32	None	Urticaria	120

HCW, Healthcare worker; Industry, latex gloves industry worker; Surgery, multiple surgical antecedents.

varying from 0.56 to 4.84 kU/L. When the recommended cutoff of 0.35 kU/L was used, the assay results were positive in all patients and in 24 of 36 control subjects (12 atopic, 12 nonatopic; specificity = 33%). A positive correlation between the Immuno-CAP and ALaSTAT-RIA assays was observed ($r = 0.90$). A dose-dependent inhibition between 0.1 $\mu\text{g/ml}$ and 100 $\mu\text{g/ml}$ ranging up to 86% was also observed.

Latex skin test

SPT responses were positive in 26 of the 38 patients (68%). Additional intradermal test responses in the 12 patients with a negative SPT response were positive in 11 and yielded a sensitivity of 97%. The specificity of our

skin test was 100%, and no adverse reactions were observed.

Latex LTT

In control subjects, the median of the cpm values was 1951 (range, 324 to 5282), and the median of the SI values was 1.34 (range, 0.69 to 13.14). In patients, the median of the cpm values was 7408 (range, 913 to 65,808), and the median of the SI values was 2.90 (range, 0.77 to 40.38). Fig. 2 shows the individual SI values in patients and control subjects. Patients had significantly higher SI values when compared with nonatopic control subjects ($p = 0.005$). However, only 15 of 38 patients had a positive SI value (sensitivity =

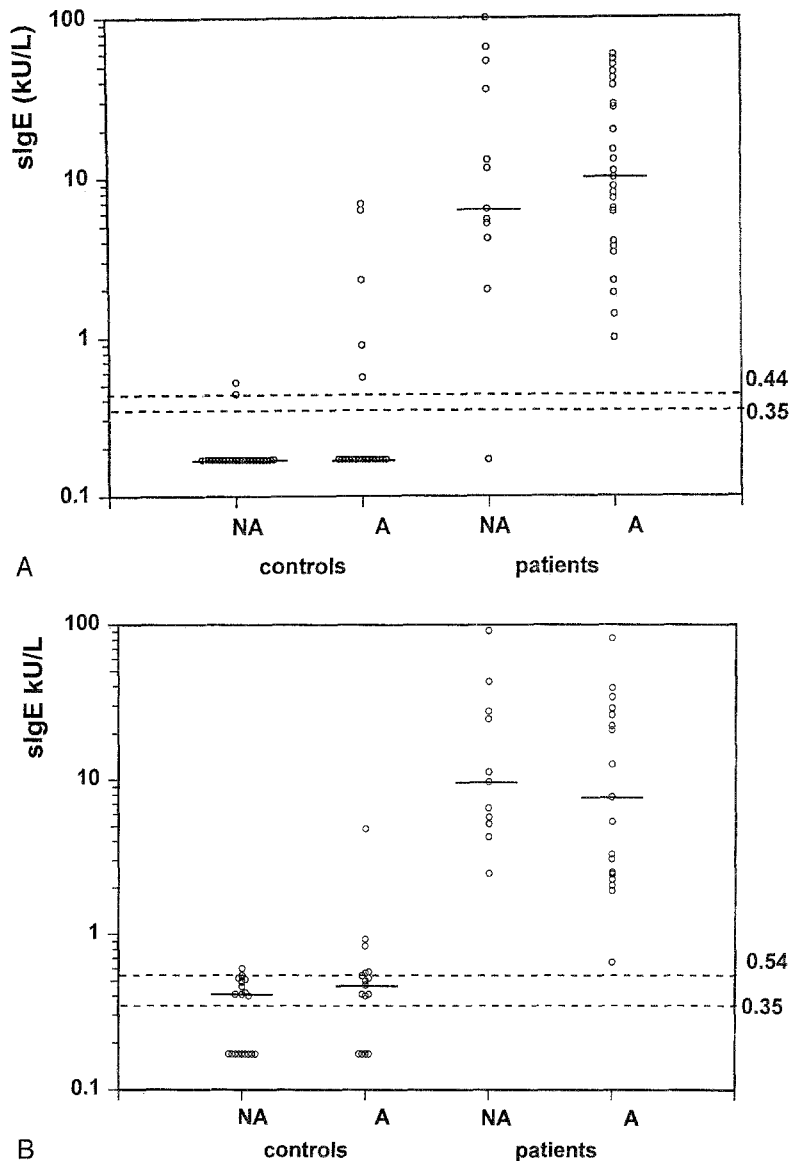


FIG. 1. Latex-specific IgE (slgE) levels in nonatopic (NA) and atopic (A) control subjects and patients. Levels are determined by Immuno-CAP (A) and ALaSTAT-RIA (B) assays.

39%, Table II). A positive SI value was almost exclusively observed in patients with serum latex-specific IgE (14 of 15 for Immuno-CAP and 11 of 12 for ALaSTAT-RIA) exceeding 3.5 kU/L. There was no correlation between latex-specific IgE levels and the SI values. No association between SI values and symptomatology was observed.

DISCUSSION

The first objective of this study was to evaluate the discriminative value of latex-specific IgE determination, the latex skin test, and the LTT test to latex between patients with latex allergy and control subjects. A second aim was to evaluate the proposed positive thresholds for latex-specific IgE measured by the Upjohn-Pharmacia CAP System and the ALaSTAT-RIA assay. Latex al-

lergy was confirmed to be more prevalent in female subjects than male subjects (35 vs 3, respectively). Almost 70% of our patients were health care workers, but in 20% of the patients no clear risk factor was identified. Serologic methods for the detection of latex-specific IgE have been proposed as the initial test for establishing the diagnosis of latex allergy.⁹⁻¹² Unfortunately, several techniques for estimation of latex-specific IgE levels were reported to be inadequately sensitive, especially when performed in health care workers.¹³⁻¹⁵ Our results indicate that the two commercially available latex-based serologic assays (Immuno-CAP and ALaSTAT-RIA) are as specific and more sensitive than the paper-disk RAST, which has been reported to identify 50% to 60% of persons with latex allergy.¹⁶ According to the 95th percentile of our nonatopic control subjects, both assays

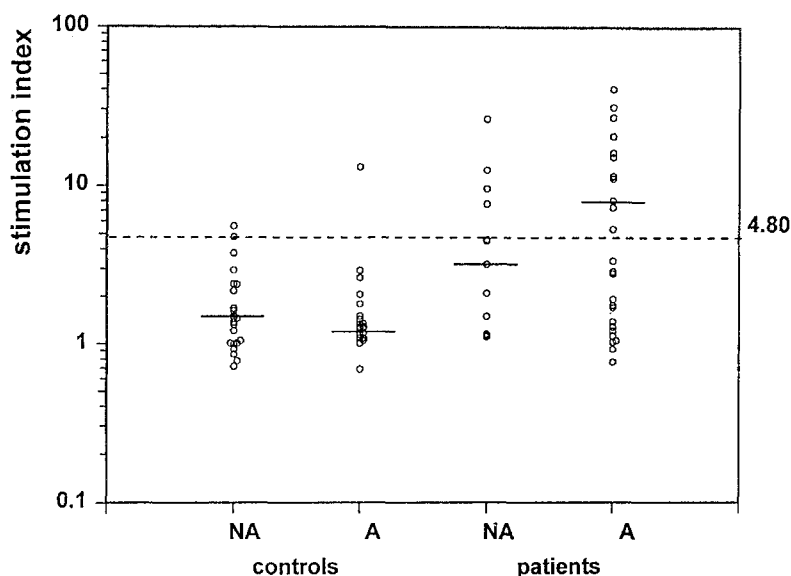


FIG. 2. Lymphocyte transformation test to latex in nonatopic (NA) and atopic (A) patients and control subjects. Results are expressed as SIs (i.e., cpm of the latex-stimulated lymphocytes divided by cpm of the lymphocytes cultured with AIM-V medium). Individual response exceeding 4.80 (95th percentile SI value of nonatopic control subjects) is considered positive.

TABLE II. Number of positive results of latex-specific IgE, skin test, and LTTs to latex in patients and control subjects

Method threshold	CAP (0.44 kU/L)	CAP (0.35 kU/L)	ALaSTAT (0.54 kU/L)	ALaSTAT (0.35 kU/L)	Skin test (3 mm)	LTT (4.8 [SI])
All patients	37/38	37/38	31/31	31/31	37/38	15/38
Nonatopic	11/12	11/12	11/11	11/11	11/12	4/12
Atopic	26/26	26/26	20/20	20/20	25/26	11/42
All controls	6/44	7/44	6/36	24/36	0/44	2/44
Nonatopic	1/24	2/24	1/20	12/20	0/24	1/24
Atopic	5/20	5/20	5/16	12/16	0/20	1/20

had a sensitivity exceeding 97% and a specificity of approximately 85%. However, the specificity of both measurements was clearly lower in atopic subjects than in nonatopic subjects. Several manufacturers and authors^{17, 18} have recommended the positive cutoff of 0.35 kU/L for the serologic assessments of latex-specific IgE. In our series, according to this threshold, the Immuno-CAP assay achieved good sensitivity and specificity. For the ALaSTAT-RIA assay, although sensitivity remained high, the specificity dropped to 33%. Ownby et al.,¹⁸ observed a discrepancy between the Immuno-CAP and ALaSTAT-RIA results. In the absence of clinical data or skin test data, however, the authors were unable to evaluate the diagnostic value of both specific IgE determinations. In our study, according to a careful clinical history and skin tests, we had the opportunity to compare sensitivities and specificities of both cutoffs. It seems that the suggested 0.35 kU/L threshold is not appropriate for the ALaSTAT-RIA assay. Moreover, our results confirm that by comparing sensitivities and specificities of different cutoffs, it is possible to establish the most efficient threshold

and to improve the "diagnostic accuracy" of in vitro IgE tests, at least for some allergens.¹⁹

Skin testing performed with different extracts has been demonstrated to be quite sensitive and specific for establishing the diagnosis of latex allergy. In their large study of more than 900 health care workers, Moneret-Vautrin and Laxenaire²⁰ obtained a sensitivity of 100% and specificity of 99%. Unfortunately, anaphylaxis can occur during skin testing.⁶⁻⁹ It is generally accepted that for classical inhalant antigens, the sensitivity of the intradermal test approximates the sensitivity of the SPT by 700- to 1000-fold. For NAL in our series, when the SPT response remained negative (up to 1 µg/ml), the intradermal test was almost always able to confirm latex allergy at a concentration between 10⁻⁶ and 10⁻³ µg/ml. This suggests that for NAL the sensitivity of the intradermal test might approximate the sensitivity of the SPT by 10⁶-fold and that latex skin tests should be performed with extreme caution. Nevertheless, in our study skin testing was confirmed to be safe and efficient in establishing the diagnosis of latex allergy.

Although LTTs are classically considered as reflections of cellular immunity, positive LTT results can be obtained in typically IgE-mediated situations, probably caused by the stimulation and expansion of T-helper cells.²¹ In accordance with others,²²⁻²⁴ we confirm that patients with latex allergy have significant lymphocyte proliferation responses to NAL and that the sensitivity of the LTT is low. Moreover, there was no relation between the SI value and clinical history. Although positive lymphocyte proliferation responses were almost exclusively observed in patients with a serum latex-specific IgE exceeding 3.5 kU/L (Immuno-CAP and ALaSTAT-RIA), no significant correlation between the latex-specific IgE values and latex-specific lymphocyte response was found.

In conclusion, the Immuno-CAP and ALaSTAT-RIA assays for specific IgE determination and the latex skin test seem to be highly clinically efficient methods for corroboration of the diagnosis of latex anaphylaxis. However, according to the 0.35 kU/L threshold the ALaSTAT-RIA assay was nonspecific. This reemphasizes that for every test we should adopt a specific positive cutoff for each allergen and abandon the usually arbitrarily chosen positive thresholds of at least some in vitro IgE tests. Compared with nonatopic control subjects, patients showed a significant lymphocyte proliferation when stimulated with NAL. However, the LTT is an insensitive diagnostic procedure and can therefore not be recommended for routine clinical use.

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