

Atopy and Risk Factors for Latex Sensitization in a Selected Population

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ABSTRACT

*The value of recommending latex allergy screening in allergy departments of the Army's Hospital was studied. The purpose of the study was to evaluate whether atopy was a risk factor for latex sensitization in a specific population such as the young male soldiers of the Italian Army. The study was also aimed to assess the role of other risk factors. One thousand five hundred male subjects (1000 subjects who were atopic and 500 subjects who were nonatopic), visiting the Department of Allergology and Respiratory Physiopathology of the Army's Hospital in Bari, Italy, were enrolled into the study. The protocol included a questionnaire (symptoms of atopy, use of latex gloves and condoms and possible reactions previous surgical procedures), a clinical examination, a skin-prick test to latex and common allergens to evaluate atopy, and in part a latex challenge. Among the 1000 subjects who were atopic, 2.8% had evidence for sensitization to latex compared with 1.2% in the 500 subjects in the nonatopic group. The risk of latex sensitization was 19 times higher for subjects with a history of reactions to latex exposure and had a twofold increase for each surgical procedure and for each skin test positivity for inhalant allergens. Another risk factor was positivity to skin-prick tests for *Artemisia vulgaris*, cypress, and molds. Atopy significantly relates to an increased risk of latex sensitization. Screening is recom-*

mended in the Army's Hospital to identify latex-sensitized subjects and inform them about the risks connected with this condition. (Allergy and Asthma Proc 24:185–191, 2003)

By a historical point of view, an immediate type I immunoglobulin E (IgE)–mediated reaction first was reported by Stern in Germany in 1927.^{1,2} It was not until 1979 that Nutter³ reported the occurrence of contact urticaria from rubber gloves in a housekeeper with a skin test positivity for natural latex extracts.

Subsequently, new cases of latex hypersensitivity have been described in the literature. Besides contact urticaria, other symptoms related to latex sensitivity are rhinitis, conjunctivitis, dyspnea, generalized urticaria, and, occasionally, anaphylaxis.⁴ The majority of these reactions are induced by either rubber gloves or contact with health care services material.⁵

The problem of natural rubber latex (NRL) sensitization has been studied since 1979. An increasing number of cases of allergy have been described, and some of them arose with severe clinical features. Because latex is seemingly almost ubiquitous and commonly used, its sensitization does not involve only peculiar groups at risk, but the majority of the general population, in which the prevalence of latex allergy appears to have remained at <1%.⁶ A number of epidemiological studies emphasizes the prevalence of sensitization to NRL.^{5–14} Recently reported rates of latex sensitization, which were detected by *in vitro* tests in 1997 healthy blood donors, range from 5.4 to 7.6%,⁶ and latex sensitization in the atopic population is as high as 9.4%.⁹ *In vitro* tests are less sensitive than skin prick test (SPT). This implies that *in vitro* tests do not detect all cases of latex allergy. In addition, low concentrations of allergen-specific IgE may ap-

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pear because of cross-allergenicity to different fruits and vegetables.

However, evaluation of diagnostic test results is complicated because a definite gold standard method for diagnosing latex allergy is not available. Sensitivity and specificity of available diagnostic testing methods are determined by comparison with clinical history in the case of SPT or clinical history and/or SPT in the case of serologic testing. This approach led to a variety of sensitivities and specificities of both SPT and *in vitro* testing. In an elegant study, Blanco *et al.*¹⁵ concluded that all the evaluated natural latex extracts for SPT showed excellent sensitivity and specificity, reaching diagnostic efficiency higher than 95%. On the other hand, latex-specific IgE determination by *in vitro* methods (coated allergen particle and AlaSTAT) showed good sensitivity; but specificity and interpretation were dependent on the population considered (100% in subjects who were nonatopic and 70% in pollen control).

The aim of the present study was to evaluate whether atopy was an important risk factor for latex sensitization in a young male population: the male Italian soldiers enrolled in the 1-year Army service in addition to the volunteers. Furthermore, we explored whether latex sensitization was influenced by other risk factors.

METHODS

The study included 1500 male subjects aged 17–29 years (mean, 20.3 years) undergoing physical examination, because of respiratory complaints, for the Army's preliminary selections at the Department of Allergology and Respiratory Physiopathology of the Army's Hospital in Bari between April 1997 and November 1999.

Our protocol was authorized by the Army's Hospital and included a questionnaire that asked for symptoms of atopy, work-related as well as work-unrelated exposure to rubber latex (use of latex gloves and/or condoms), the number of previous surgical procedures, and any possible reaction associated to the exposure. After giving their informed written consent, all subjects underwent diagnostic tests and clinical evaluation.

Skin-prick tests were performed with a nonammoniated commercial extract of latex (Stallergènes, Paris, France) and with common inhalant allergens (Lofarma, Milan, Italy) including *Dermatophagoides pteronyssinus* and *farinae*, *Parietaria*, grass pollen, olive pollen, cypress pollen, *Artemisia vulgaris*, *Cladosporium*, *Aspergillus fumigatus*, and cat dander. Skin-prick tests were performed according to Pepys's method¹⁶ using histamine (10 mg/mL) and normal saline as positive and negative controls, respectively. Wheals of ≥ 3 mm were regarded as positive in the absence of a reaction to normal saline. In this study atopy was diagnosed by the presence of one or more positive skin tests for common inhalant allergens in patients with a careful clinical history of allergic rhinoconjunctivitis or asthma.¹⁷

Challenge tests were performed in subjects with positive latex SPT. Challenges were performed by wearing a finger-

tip cut from a surgical glove (Le Petit, Gradate, Como, Italy), which was dampened with water and was placed on one finger for 15–30 minutes. If the reaction was negative, the whole glove was worn for the same amount of time, whereas the vinyl glove, which was dampened with water, was placed on the other hand as control. A challenge test was regarded as positive when there were symptoms of contact urticaria, rhinitis, or asthma. The clinical ear, nose, and throat; respiratory; and cardiovascular examination was the last step of the protocol.

The association between latex sensitization and potential risk factors was evaluated by χ^2 test and Fisher's exact test when necessary. Cochran-Armitage's trend test was used to evaluate the prevalence of the latex sensitization increment in relation to the number of surgical procedures and to the number of positive skin tests.

Stepwise logistic regression analysis and multiple correspondence analysis were also performed to evaluate the effect of different risk factors on latex sensitization. Such analysis allows further graphical evaluation of the spotted association. Statistical analysis was performed by the SAS 6.12 statistical software (SAS Institute, Inc., Cary, NC).¹⁸

RESULTS

Based on a questionnaire, all subjects reported respiratory atopic symptoms, but after skin testing with common inhalant allergens 1000 consecutive men were selected and classified as atopic. The remaining 500 subjects were classified as nonatopic after skin testing and were used as the control group.

Univariate Analysis Results

Table I reports the distribution of the 1500 examined subjects in relation to both latex sensitization and risk factors. By evaluating the 34 latex-sensitized subjects' clinical pattern with the 1466 nonsensitized subjects', we found that the following factors increased the probability of individual sensitization to latex:

- Atopy. Among the 1000 positive subjects for at least one of the tested inhalant allergens, 28 subjects (2.8%) also had sensitization to latex compared with 6 subjects (1.2%) identified within the group of subjects who were nonatopic ($\chi^2 = 3.85$; $p = 0.05$; odds ratio [OR] = 2.37; confidence interval [CI], 0.97–5.76).
- Symptoms of latex exposure. Among the subjects, 21.4%, reporting reactions to latex exposure in their history, were sensitized to latex, whereas 1.9% of non-reactive subjects were actually positive ($\chi^2 = 47.25$; $p = 0.001$; OR = 14.06; CI, 5.29–37.37).
- Previous contacts with latex gloves and/or condoms. Among subjects, 3.5% had a positive SPT for latex as compared with 1.5% of subjects without previous exposure ($\chi^2 = 6.59$; $p = 0.01$; OR = 2.40; CI, 1.20–5.43).
- Surgical procedures. As shown in Table I, the prevalence of latex sensitization increases as the number of surgical

TABLE I

**Distribution of the 1500 Examined Subjects as Related to Latex Sensitization
and the Different Potential Risk Factors**

Risk Factors	Patients (n = 1500)	Latex-Nonsensitive Patients (%) (n = 1466)	Latex-Sensitive Patients (%) (n = 34)	p Value*
Atopy				
No	500	494 (98.8%)	6 (1.2%)	0.05
Yes	1000	972 (97.2%)	28 (2.8%)	
Symptoms to latex exposure				
No	1471	1443 (98.1%)	28 (1.9%)	0.001
Yes	28	22 (78.6%)	6 (21.4%)	
Contacts with latex gloves and/or condoms				
No	934	920 (98.5%)	14 (1.5%)	0.01
Yes	566	546 (96.5%)	20 (3.5%)	
No. of surgical procedures				
0	1016	1001 (98.5%)	15 (1.5%)	0.003
1	410	396 (96.6%)	14 (3.4%)	
2	58	55 (94.8%)	3 (5.2%)	
≥3	15	13 (86.7%)	2 (13.3%)	
No. of positive allergens to skin test				
0	500	494 (98.8%)	6 (1.2%)	0.001
1	267	265 (99.2%)	2 (0.8%)	
2	284	281 (98.9%)	3 (1.1%)	
≥3	449	426 (94.9%)	23 (5.1%)	
Positive allergens				
<i>Dermatophagoides</i>				
No	787	777 (98.7%)	10 (1.3%)	0.007
Yes	713	689 (96.6%)	24 (3.4%)	
Grasses				
No	1000	990 (99%)	10 (1%)	0.001
Yes	500	476 (95.2%)	24 (4.8%)	
<i>Artemisia vulgaris</i>				
No	1303	1290 (99%)	13 (1%)	<0.0001
Yes	197	176 (89.3%)	21 (10.7%)	
Olive pollen				
No	1108	1096 (98.9%)	12 (1.1%)	0.001
Yes	392	370 (94.4%)	22 (5.6%)	
Cypress pollen				
No	1407	1393 (99%)	14 (1%)	<0.0001
Yes	93	73 (78.5%)	20 (21.5%)	
<i>Parietaria</i>				
No	1203	1191 (99%)	12 (1%)	0.001
Yes	297	275 (92.6%)	22 (7.4%)	
Molds				
No	1386	1372 (99%)	14 (1%)	<0.0001
Yes	114	94 (82.5%)	20 (17.5%)	
Cat dander				
No	1171	1161 (99.2%)	10 (0.8%)	0.001
Yes	329	305 (92.7%)	24 (7.3%)	

One subject's data are missing (for symptoms to latex exposure and surgical procedures).
 χ^2 test and Fisher's exact test when necessary.

procedures grows ($\chi^2 = 18.8$; $p = 0.0012$; Cochran-Armitage's trend test $z = 3.71$; $p = 0.0001$)

- Polysensitization (described in the Table I by the variable of

the number of positive allergens). Influenced the latex sensitization showing an increasing trend ($\chi^2 = 24.41$; $p = 0.001$; Cochran-Armitage trend test $z = 3.74$; $p < 0.0001$).

TABLE II

Results of Logistic Regression Analysis

	Parameter Estimate	p Value	OR
1st Model			
Intercept	-7.09		
Symptoms with latex exposure	2.93	0.0001	18.69
No. of surgical procedures	0.67	0.009	1.96
No. of positive allergens	0.83	0.0001	2.3
2nd Model			
Intercept	-6.03		
Symptoms with latex exposure	3.53	0.0001	34.05
No. of surgical procedures	0.64	0.02	1.9
Molds	2.32	0.0001	10.17
Cypress pollen	2.51	0.0001	12.31
<i>Artemisia vulgaris</i>	1.22	0.01	3.38

1st Model: Hosmer and Lemeshow goodness of fit test = 56.052; $p < 0.001$.

2nd Model: Hosmer and Lemeshow goodness of fit test = 5.83; $p = 0.05$.

Variables were selected by stepwise procedures; the following were variables evaluated at the beginning:

1st Model. Symptoms to latex exposure, number of surgical procedures, number of skin test positivity to inhalant allergens, and use of latex gloves and/or condoms

2nd Model. Symptoms to latex exposure, number of surgical procedures, skin test positivity to single allergens (cat dander, molds, Parietaria, cypress pollen, olive pollen, *Artemisia vulgaris*, grasses, Dermatophagoides)

Logistic Regression Analysis Results

Table II shows the results of two logistic regression models. The first model was constructed by using latex sensitization as a function of four factors: (a) previous reactions to latex exposure, (b) number of surgical procedures, (c) number of skin test positivities for inhalant allergens, and (d) use of latex gloves and/or condoms. Only the first three factors were significant and therefore were included in the model. The variable "contact with latex gloves and/or condoms" was a significant risk factor for latex sensitization in univariate analysis. However, in multivariate logistic regression analysis it did not reach statistical significance, perhaps because this variable is included in other variables such as "symptoms to latex exposure" and "surgical procedures."

By examining the OR it is possible to consider the following:

1. The risk of latex sensitization for subjects who had previous symptoms to latex exposure is ~ 19 times higher than the one for nonreactive subjects (OR = 18.7).

2. The risk of latex sensitization showed a twofold increase with each surgical procedure (OR = 1.96).
3. The risk of latex sensitization exhibited a twofold increase at each skin test positivity for inhalant allergens (OR = 2.3).

Even though the first model adequately fits all data (Hosmer and Lemeshow test = 56.05; $p < 0.001$), to find the allergens showing a major impact on the risk of latex sensitization, we constructed a second model in which the number of positive allergens to skin tests was substituted by the positivity to individual skin tests as a variable. This model shows significance for the following allergens: molds, cypress, and *A. vulgaris*.

Multiple Correspondence Analysis Results

Figure 1 shows the results of multiple correspondence analysis. The first two dimensions, represented by each individual axis, explain the 35.2% of variance and show a definite opposition between data included into quadrants on the right (I and II) and data included into quadrants on the left (III and IV).

The I and II quadrants are related to skin test positivity for inhalant allergens, the presence of latex contacts, latex reactions, and previous surgical procedures as well as a positive skin test response to latex; the III and IV quadrants include opposite characteristics: negativity of skin test responses to common inhalant allergens and latex, absence of latex contacts and reactions, and previous surgical procedures. Furthermore, it is interesting to observe that by correspondence analysis, cypress, molds, and *A. vulgaris* allergens (*i.e.*, the allergens that were significant in the second model of logistic regression) occurred in a position close to the one of the positivity to latex. The concordance between the risk factor distribution and the one relative to latex sensitization confirms, on the multivariate analysis, the association between the considered factors, which was already shown by the results of the previous analysis (Tables I and II).

Challenge Test

Finally, latex challenge was positive in 17/34 latex SPT-positive subjects. The main characteristics of positive latex challenge and negative latex challenge are presented in Table III.

DISCUSSION

In our study the prevalence of sensitization to latex was 2.8% in subjects who were atopic and 1.2% in subjects who were nonatopic. The major prevalence should be related to the fact that atopy is an important and well-known risk factor for latex sensitization. Moneret-Vautrin *et al.*⁹ reported percentages of latex sensitization of 9.4% in patients who were atopic and of only 0.4% in patients who were nonatopic. Furthermore, Porri *et al.*¹⁰ have shown a prevalence of latex sensitization as high as 11.2%

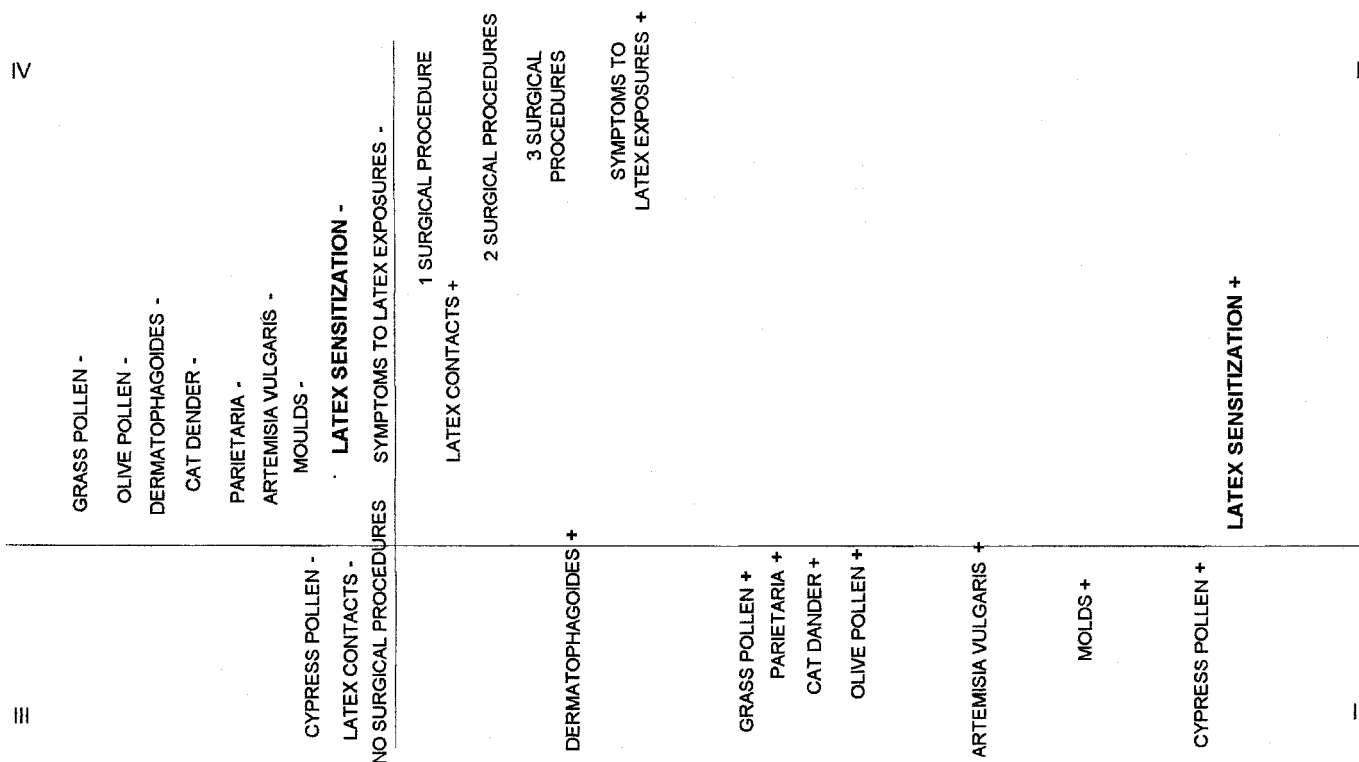


Figure 1. Results of multiple correspondence analysis. The characteristics of the population are described by the first two dimensions (35.21% of variance): quadrant I and II are related to positivity (+) to latex sensitization, inhalant allergens skin test, latex reactions, and surgical procedures; quadrant III and IV are related to negativity (-) of the same characteristics.

in patients who were atopic compared with 2.8% in patients who were nonatopic. One study about intensive care unit operators performed by Watts *et al.*⁵ reported a prevalence of latex sensitization of 35% and 3.7% in subjects who were atopic and nonatopic, respectively. In these quoted studies, the prevalence of latex allergy was higher than in our study, because we considered a selected population that was not frequently in contact with NRL products. In addition, in our study, latex sensitization was evaluated only by SPT positivities, whereas in other studies, *in vitro* tests were performed too.

An association between atopy and high probability of latex sensitization was found in a report by Bernardini *et al.*¹¹ in children's school. Our study confirmed that atopy is an important factor for latex sensitization even in a young male population, as well as the well-known categories of risk-associated subjects.

Our study also evaluated the influence of other factors on latex sensitization and identified some conditions related to the risk of sensitization: a positive history for previous latex reactions or previous surgical procedures; the positivity to a skin-prick test for cypress pollen, *A. vulgaris* pollen, or molds, and, furthermore, polysensitization, *i.e.*, skin test positivity for two or more inhalant allergens.

In our study, 21.4% of subjects who had described previous reactions to latex were highly sensitized as compared with 1.9% of subjects with no positivity in their history.

Porri *et al.*⁸ described that out of eight children who had undergone previous surgical treatments, seven children who were studied by symptoms of allergy after exposure to latex were positive to the skin test for latex. Therefore, the occurrence of previous adverse reactions to latex represents a risk factor, which increases the possibility of sensitization to latex. In our work, this was 19 times higher as compared with those studies that did not mention such condition in their history.

Several reports have described that spina bifida children are at higher risk for latex sensitization. Porri *et al.*⁸ reported a higher tendency to latex sensitization in these patients, which was potentially related to the surgical procedures and not to genetic factors. In fact, no substantial differences were observed between spina bifida children and those children with a history of several surgical procedures. On the other hand, this finding also was established by other investigators.^{12,13} In our study, 3.9% of subjects treated with surgical procedures were sensitized to latex compared with 1.4% of the individuals who have not undergone any previous surgery. In particular, each surgical procedure gave a twofold increase of such risk at an extent similar to the one already shown by Lee *et al.*¹⁴ in spina bifida patients.

Another element of our study concerns the polysensitization for common inhalant allergens as a possible risk factor. Latex might be a ubiquitous antigen, because it is released

TABLE III

Main Characteristics of Challenge-Positive Patients and Challenge-Negative Patients

	Challenge Positive (n = 17)		Challenge Negative (n = 17)	
	No.	%	No.	%
Symptoms to latex exposure	6	35.3	0	
Contacts with latex gloves and/ or condoms	16	94.1	4	23.5
No. of surgical procedures				
0	2	11.8	13	76.5
1	10	58.8	4	23.5
2	3	17.7	0	
≥3	2	11.8	0	
No. of positive allergens on skin testing				
0	2	11.8	5	29.4
1	1	5.9	0	
2	2	11.8	1	5.9
≥3	12	70.6	11	64.7
SPT positivities				
<i>Dermatophagoides</i>	12	70.6	12	70.6
Grasses	13	76.5	11	64.7
<i>Artemisia vulgaris</i>	10	58.8	11	64.7
Olive pollen	11	64.7	11	64.7
Cypress pollen	9	52.9	11	64.7
<i>Parietaria</i>	11	64.7	11	64.7
Molds	9	52.9	11	64.7
Cat dander	12	70.6	12	70.6
Atopy	15	88.2	13	76.5

in small particles by car tires,¹⁹ but whether this form of latex is allergenic is unproved. This twofold increase for each positivity to individual allergens was analogous to the twofold increase after each surgical exposure.

Finally, our study showed a clear relationship between the increased probability of latex sensitization and the positivity to SPT for inhalant allergens (*A. vulgaris* and cypress pollen and molds). Fuchs *et al.*²⁰ identified a high molecular weight cross-reactive glycoprotein allergen in *A. vulgaris* pollen and in latex. The described occurrence of common epitopes could explain the association between latex sensitivity and skin test positivity for this allergen.

Furthermore, cross-reactivity between cypress pollen and bromelain, which is a glycoprotein contained in pineapple, was shown, and this was related to some carbohydrate epitopes, which were sensitive to treatment with periodate.²¹ However, the established cross-reactivity between bromelain and papain,²² which is another protease that cross-reacts with latex,²³ could indirectly explain the association of the positivity to prick testing with cypress with the sensitization to latex.

Enolases such as the Cla h 6 allergen of *Cladosporium herbarum*,²⁴ and manganese-containing superoxide dis-

mutases such as the Asp f 6 allergen of *A. fumigatus*²⁵ are important mold allergens. Recently, the Hevea latex enolase was accepted as Hev b 9 and the latex manganese-containing superoxide dismutases was accepted as Hev b 10 by the Allergen Nomenclature Committee. This could possibly explain the relationship between the development of sensitization to latex and to molds.

The latex challenge was found to be positive in 50% of latex-sensitized subjects. This percentage is lower than reported in previous studies.^{26–30} These different percentages could depend on many factors:

- The use test could be conclusive in patients with allergic skin disease. However, it may yield negative results in patients with respiratory and ocular symptoms. To rule out asthma or rhinoconjunctivitis related to latex, specific provocation tests should be made.
- Probably the low percentage of glove test positivity in our study may be explained by the fact that the provocation tests were not performed on the high-risk group of patients (because of frequent contacts with NRL products) because they were performed in other workers (spina bifida patients and health care workers).
- Criteria used to define use test positivity could be different.
- Different amount of allergens in gloves used in the tests.
- In addition, the low percentage of use test positivity could be explained by the different allergenic epitopes, which is present in commercial extracts used in SPT, and in the gloves used in the provocation test.

In conclusion, although in a young-aged population, the prevalence of latex sensitization in our study (2.8% among the subjects who were atopic and 1.2% among the subjects who were nonatopic) suggested an important result. In fact, there are individuals, who are sensitized to latex and who ignore this condition and therefore are exposed to the development of some even severe allergic reactions, particularly in the setting of surgical or diagnostic procedures.³¹

Skin-prick tests for latex allergy are not beyond reproach, notwithstanding their broad acceptance. The lack of an approved latex extract and the choice of the test reagent and their different allergenic potencies are the major disadvantages of this diagnostic method. In fact, the allergen source in the case of SPT is commonly natural rubber extract, as well as in this study (high sensibility and specificity, Stallergènes).³² However, subjects encounter latex products more frequently. Only a small proportion of latex proteins may be present in finished products such as gloves. In addition, novel epitopes arise in the course of manufacturing.

In addition, using NRL product extracts (*e.g.*, glove extract) in place of latex preparations does not resolve all the issues because different brands of gloves are variable in the relative content and composition of the individual latex allergens. After all, SPT positivities could establish not

necessarily latex sensitization, but sensitization to cross-reacting foods or inhalant allergens.

We believe that systematic screening, which may be performed in allergy departments like those of the Army, notwithstanding aforementioned limitations, may allow rapid identification of those subjects and inform them about the risks connected to this condition.

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