

Assessment of latex allergy in a healthcare population: are the available tests valid?

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Summary

Background Latex allergy can cause serious, preventable work-related health problems in healthcare workers who are a high risk group for this form of allergy. Type I hypersensitivity can produce life-threatening systemic effects, and involves an allergen-specific immunoglobulin (IgE) response to proteins found in latex. The estimated prevalence of latex 'allergy' in healthcare workers varies widely (2.8% – 18%), and studies do not always distinguish between those who are positive in an assay for latex-specific IgE and those with clinical allergy.

Objective To assess the performance of four *in-vitro* methods and three skin testing methods for detecting latex-specific IgE in a group of UK healthcare workers. Test results were compared with reported clinical symptoms defined by questionnaire.

Methods Skin prick testing was carried out on volunteers using three reagents: (a) stallergenes commercial latex extract (Cedex, France); (b) an in-house latex glove extract; and (c) a fresh glove piece. Specific IgE levels were determined using Pharmacia AutocapTM (Uppsala, Sweden), Pharmacia UnicapTM (Uppsala, Sweden), DPC Immulite[®] (Los Angeles, USA) and Hycor HytecTM (Irvine, California, USA) methods. Each volunteer completed a questionnaire detailing latex exposure and allergic history.

Results *In vitro* methods for detecting specific IgE to natural rubber latex were positive in 3.6%, to 43.6% of the same population. Skin prick tests positivity varied between 2.9% and 14.3% with different extracts. From the subjects tested 9.1% reported symptoms which could be consistent with type I allergy, although none had been given a pre-existing diagnosis of latex allergy, and 43.6% of volunteers reported symptoms consistent with type IV hypersensitivity or irritant dermatitis.

Contingency tables and chi-squared analysis revealed no correlation between most methods. No correlation was shown between symptoms consistent with type I allergy and any *in vitro* or skin testing method for latex-specific IgE.

Conclusions A wide variation between testing procedures was found, and no method could be correlated with reported symptoms of type I allergy. At least one *in vitro* specific IgE assay produced a high percentage of positive results at variance with the clinical symptoms in volunteers. A clinical history is essential in establishing type I hypersensitivity to latex and test results should not be used in isolation. The incidence of clinical sensitization may be seriously over-estimated if only laboratory parameters are used.

Keywords: latex, allergy, skin prick testing, specific IgE assay, healthcare workers

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Introduction

Healthcare workers are a 'high risk' group for type I latex allergy owing to daily exposure to latex products (e.g. disposable gloves) [1–5]. The estimated prevalence of latex allergy among healthcare workers varies widely, from 2.8 to 18% [6–7]. It is however, thought that latex allergy affects only 0.12% of adult surgical patients and 0.4% of nonatopics in some allergy clinics [6]. If the level of latex allergy in healthcare workers is as high as reported in some studies, this is a major public health concern with important implications for the NHS. However, there are serious concerns regarding the lack of standardization of the diagnostic tests available, and their clinical validation is often uncertain.

The most common form of reaction to latex is a non-immunological irritant contact dermatitis, which may be attributed to the cornstarch powder lubricant or to physical maceration and humidity of the gloved hand [8]. The most common 'allergic' reaction is type IV (delayed) hypersensitivity, to the residues of accelerator and plasticiser agents added during latex processing [8]. The existence of type IV hypersensitivity to natural rubber latex proteins is controversial. The least common, but potentially most serious, form of reaction is type I hypersensitivity. This is an IgE-mediated immediate-type reaction to extractable proteins from natural rubber latex. These have been partially characterized [6]. IgE-mediated reactions may include urticaria, angioedema, rhinoconjunctivitis, asthma and on rare occasions life-threatening systemic anaphylaxis [9].

Correct diagnosis of latex type I allergy is very important since it has occupational health and surgical implications [10,11]. This study examined the performance of commonly used techniques for detecting latex-specific IgE in a group of healthcare workers who are potentially at high risk for this form of hypersensitivity, but none of whom carried a pre-existing diagnosis of latex allergy. Four tests for latex-specific IgE *in vitro* (from serum samples) and three skin prick tests (SPT) with different latex preparations were used. The test results were compared with reported clinical symptoms. It is important to distinguish between those individuals merely positive in an assay for latex-specific IgE and those with symptoms of clinical allergy, because for most tests for allergen-specific IgE there are a proportion of healthy individuals who are positive, without obvious clinical symptoms, and the presence of a positive test is not a reliable indicator of risk of future events. Furthermore there are unresolved technical issues regarding the standardization of tests, and the result using one technology may be quite different in another, confounding estimation of prevalence. This study highlights the surprising lack of standardization; the difficulties in interpreting the results of individual assays in an

unselected survey of health care workers in a UK hospital; the importance of using a well validated and standardized testing protocol; and the pre-eminent role of the clinical history in the diagnosis of latex allergy.

Materials and Methods

Fifty-five volunteers were recruited with informed consent from the laboratory, medical, nursing and ancillary staff of the Northern General Hospital, Sheffield. No selection for people with perceived problems with latex was made. The study was approved by the North Sheffield Research Ethics Committee. Blood samples were taken from all 55 healthcare workers; 35 volunteered for additional skin prick tests. All completed a questionnaire detailing latex exposure and allergic history, designed to elicit symptoms of potential type I allergy (Group 2), type IV allergy or irritant contact dermatitis (Group 3) or no symptoms (Group 1). Group 2 included volunteers who reported having an urticarial rash less than 24 h after contact with latex or itchy eyes/runny nose/sneezing/shortness of breath. Those who reported itchy nonurticarial rash of onset at later than 24 h, without other symptoms, were classed as Group 3. All individuals with an appropriate clinical history were offered allergy consultation for definitive investigation, but all refused on the basis that their symptoms were not unduly troublesome. Direct confirmation of allergy by challenge was therefore not possible. None had symptoms of severe anaphylaxis or bronchospasm.

Volunteers were classed as atopic if they had more than one SPT positive result to HDM, grass and cat allergen (one volunteer classed as atopic was SPT positive for grass, egg and feathers; HDM and cat were not tested). Latex-specific IgE levels were determined using *in vitro* assay A (Pharmacia AutocapTM, Uppsala, Sweden), assay B (Pharmacia UnicapTM, Uppsala, Sweden), assay C (DPC Immulite®, Los Angeles, U.S.A.) and assay D (Hycor Biomedical Inc. HytecTM, Irvine, California, USA). These represent commonly used technologies in the UK. Each test was carried out following the manufacturer's instructions.

The levels of specific IgE were graded as follows according to the manufacturer's recommendations (Table 1).

Table 1. Grading of specific IgE levels

Grade	IgE IU/mL	Assays	Interpretation
0	<0.35	A, B, C, D	negative
1	0.35–0.69	A, B, C, D	weak positive
2	0.7–3.49	A, B, C, D	positive

Assays A, B, C and D included standards which were calibrated against the WHO 2nd International reference preparation for human serum IgE 75/502. No values greater than grade 2 were seen.

Skin Prick Testing (SPT)

A total of 35 out of 55 healthcare workers were assessed for latex allergy by means of SPT. This was carried out in a consistent manner using standard techniques, by an experienced clinician. Method 1 used a commercial 'standardized' latex extract (Stallergenes, Cedex, France), method 2 used an in-house latex extract which was prepared according to previously published methods [5] from Ansell Conform gloves, and method 3 used a fresh 2×2 cm glove piece (using the same glove as for the extract). Powdered Ansell Conform gloves were chosen owing to their availability and relatively high levels of allergen and protein compared to other available brands [11], and because none of the very high allergen level gloves are in use at the Northern General Hospital. The extractable allergen level in Ansell conform gloves in certain batches is reported to be 126 AU/mL and the extractable protein is between 76 and 124 µg/mL [12]. The same batch as used in previously published studies was not available, and batch to batch variation is a possibility. However this method does replicate a common clinical practice. A histamine (10 mg/mL) positive control and a negative control of physiological saline was used. A mean weal diameter of greater than or equal to 3 mm with a flare of more than 10 mm was considered positive. Borderline positive was defined as a mean weal size of 2–3 mm with a flare of at least 5 mm mean diameter, or a weal of at least 3 mm without a flare or with a flare of less than 10 mm. In this respect our definition of positivity is more strict than that of many allergists who regard weals of 3 mm or greater as positive irrespective of flare. We classify these as borderline. SPT was also carried out for house dust mite (HDM), grass pollen and cat (Bencard reagents, Smith Kline Beecham Pharmaceuticals, Welwyn Garden City, Herts, UK) to confirm the atopic state of the volunteer. Antihistamines were not taken by any of the volunteers in the 48 h prior to the test.

Statistics

A comparison was performed statistically by a two-way analysis of variance—randomized complete block design. The least significant difference (LSD) method was used to establish where the differences lay between the methods.

Contingency tables (tests of association) were used to establish if there was any association between positive test results for latex-specific IgE and symptom Groups 1–3. Yates correction was used in cases where the degrees of freedom (v) = 1.

Results

Questionnaire response

The majority of respondents were female ($n = 42$, 76.3%), aged 20–40 ($n = 36$, 65.4%) and were pathology laboratory staff ($n = 26$, 47.2%) or nurses/medical staff ($n = 19$, 34.5%). All volunteers used latex gloves daily—40% reported wearing gloves 3–4 h total per day and 36.4% of volunteers indicated that they change gloves >8 times per day.

Statistics

There were considerable differences between each assay. Assay A produced positive results in four (7.3%) volunteers, assay B in two (3.6%), assay C in seven (12.7%) and assay D in 24 (43.6%). Two-way analysis of variance was used to compare the grades and IU/mL values in the four *in vitro* techniques. Assay D method is significantly different from the assays A, B and C (using the least significant difference method). No statistical difference between the other three methods could be shown.

Test results vs clinical history

The results were analysed in relation to each symptom group (Fig. 1a–f, Table 2). Only five (9.1%) volunteers reported symptoms which could be consistent with type I hypersensitivity (Group 2), but all refused further investigation and challenge owing to the mild nature of their symptoms. Twenty-four (43.6%) volunteers reported symptoms consistent with type IV or irritant contact dermatitis (Group 3) and 26 (47.3%) of volunteers reported no symptoms on latex exposure (Group 1).

No association between the clinical symptoms that would indicate a possible type I allergy (Group 2) and test results from any method could be shown, whether all individuals with Grade 1-specific IgE assay or borderline SPT were included or excluded from the analysis. A weak association between assay C and volunteers with symptoms consistent with type IV allergy/irritant contact dermatitis (group 3) was shown ($P = 0.046$), but there was no association between this group and any other method.

Comparison of methods

An association between assays A and B was shown ($P = 0.0002$) which was not surprising since they are essentially the same assay, but no correlation between any other *in vitro* methods could be shown. A weak association between SPT method three and *in vitro* assay A was found ($P = 0.03$), but no relationship between any other SPT

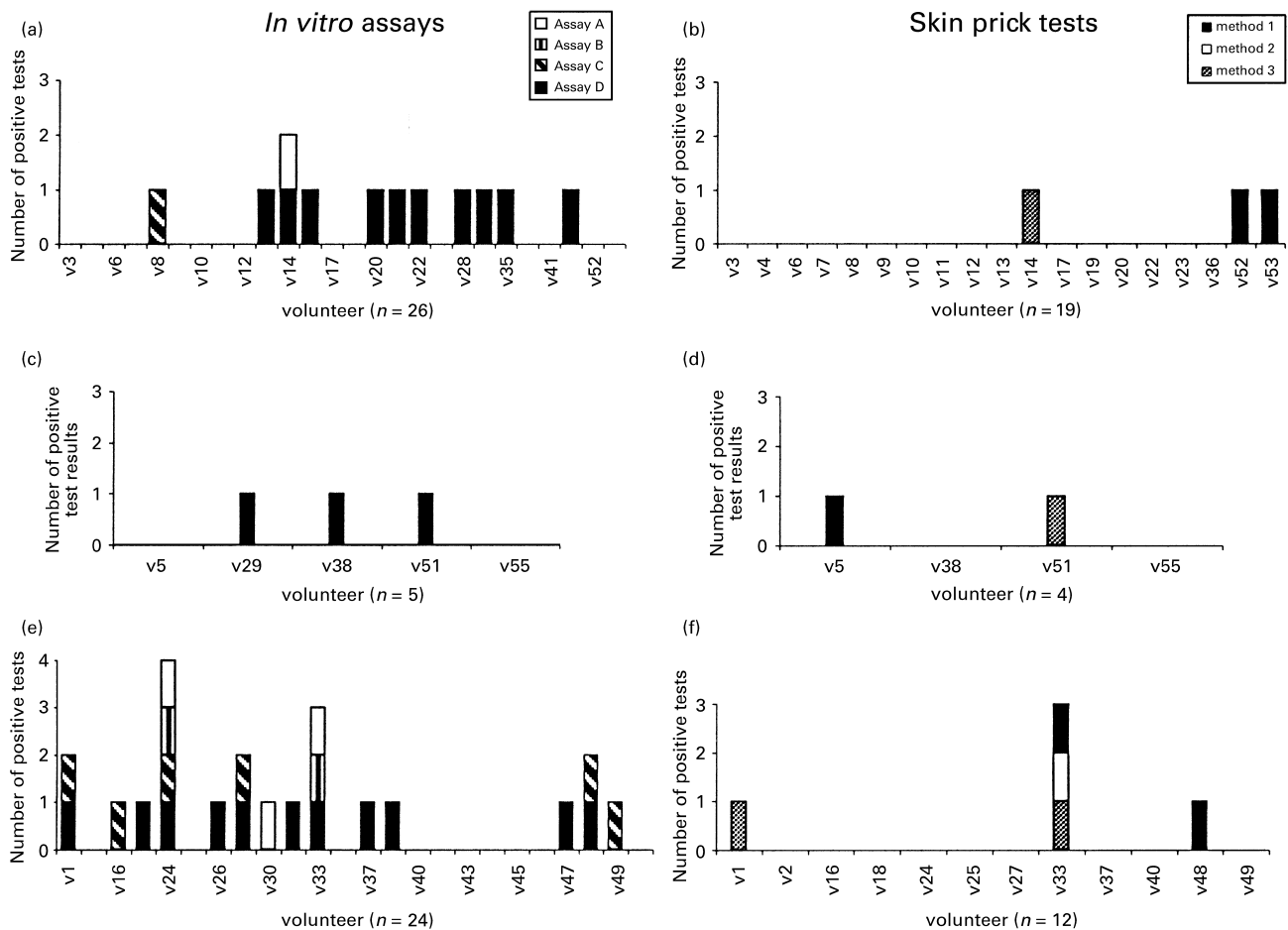


Fig. 1. The distribution of positive or borderline positive test results for latex specific IgE in volunteers without symptoms (Group 1; a,b), with symptoms of potential type 1 allergy (Group 2; c,d) and with symptoms suggesting type IV allergy (Group 3; e,f).

method and *in vitro* method could be demonstrated. No association between SPT results could be demonstrated.

Positive results in each cohort

In vitro tests From 26 subjects, 11 (42%) of Group 1 asymptomatic volunteers were positive (Grade 1 or 2) in at least one *in vitro* test (Table 2), in contrast to 3/5 (60%) of Group 2 volunteers with potential type 1 allergy, and 14/24 (58%) of Group 3 volunteers with potential late onset dermatitis.

Five individuals had a specific IgE test of grade 2 in at least one of the four *in vitro* assays, but only one individual (V24, Group 3) was positive in all four assays (but not in any SPT). Two others were grade 2 positive in one *in vitro* method, in the absence of any other positive *in vitro* test.

If the *in vitro* assay results for the most 'sensitive' assay D are excluded, 3/26 (12%) of Group 1, 0/5 (0%) of Group 2

and 8/24 (33%) of Group 3 individuals were positive in any in-vitro assay (Grade 1 or 2) (Fig. 1a,c,e).

Skin tests Borderline or true positive skin tests were seen in 3/19 (16%), Group 1 (2/3 borderline), 2/4 50%, Group 2 (both borderline) and 3/12 (25%) Group 3 (1/3 borderline). (Fig. 1b, d, f), Only one asymptomatic individual (V33, group 3) was clearly positive in all three SPT techniques (and this individual was also positive in three of the four *in vitro* assays, two at grade 1 and one at grade 2) (Table 1).

Results in atopic individuals

14/35 (40%) of volunteers were classed as atopic, i.e. had more than one other SPT positive result to HDM, grass and cat allergen (one volunteer classed as atopic was SPT positive for grass, egg and feathers; HDM and cat were not tested). 8/16 (50%) of volunteers who gave positive *in vitro* results to latex were classed as atopic. One hundred percent

Table 2. Detailed comparison of the test results and clinical symptoms in volunteers with positive tests for specific IgE to latex

	Assay A IU/ml	Assay B IU/ml	Assay C IU/ml	Assay D IU/ml	SPT 1 mm weal (flare)	SPT 2 mm weal (flare)	SPT 3 mm weal (flare)	Atopy
Group 1			1.6	0.38				
	0.4			0.72			3.5 (11.5)	Y
				0.5				
				0.45				Y
				0.56				
				0.39				
				0.41				
				0.36				
				0.67				
				0.36				
					2.5 (6.5)			Y
					3.5 (4)			Y
Group 2							2.5 (33)	Y
				0.6				
				0.57				
				0.87	3 (4)			Y
Group 3			0.52	0.51			3.5 (8)	Y
			0.67					
	0.78	0.7	1.7	0.38				Y
				0.76				
			0.65	0.46				
				0.59				Y
	0.5							
				0.73				
	0.5	0.56		1.35	5.5 (15)	5 (20)	3 (19)	Y
				0.42				
				0.56				
				0.44				
			0.55	0.38	3.5 (8.5)			Y
			1.5					

(11/11) of volunteers who showed positive borderline positive SPT results to latex were atopic. Five of these 8 (63%) also gave at least one positive *in vitro* result.

Discussion

This survey of latex allergy among healthcare workers shows that the number of subjects with positive test results for latex-specific IgE to range from 2.9 to 43.6% depending on the method of assessment used. There is little agreement between any of the methods, and positive results are found in many volunteers who report no symptoms of latex sensitivity. None of the methods were associated with particular clinical symptoms.

Positive or borderline results *in vitro* are seen in 42% of

asymptomatic individuals, 60% of potential type 1 allergy and 58% of patients with dermatitis. Excluding the results from the sensitive Assay D, 33% of dermatitis patients and 8% of asymptomatic individuals were positive, but no patients with potential type 1 allergy were positive. Skin tests were positive or borderline in similar numbers of patients, but in different individuals, with 16% of asymptomatic, 50% of potential type 1 allergy, and 25% of dermatitis patients returning positive or borderline results. Atopics are over-represented in the SPT positive or borderline positive group (7/8, 88%), but appear not to be over-represented in the *in vitro* positive group (8/16, 50%). This observation raises important questions about the predictive values of skin prick or *in vitro* methods in atopic individuals regularly exposed to latex. While this small study does not

reflect the utility of the tests in a general population, nor the frequency of positivity in patients presenting with symptoms of natural rubber latex allergy to an allergy clinic, it does suggest that the assessment of latex allergy in a health-care population by currently available *in vitro* methods is not reliable, even if we acknowledge that only a proportion of the 9.1% of volunteers with symptoms of possible type I allergy may actually have IgE-mediated hypersensitivity.

Statistical testing indicated no association between assays from different sources despite apparent standardization of the assay calibrators against the same WHO reference preparation (75/502 human serum IgE). Likewise, the different SPT methods did not show any association with each other. The known variability in leachable latex proteins between different gloves, different storage conditions and times, the potential batch to batch variation in protein content [13] and uncertainties regarding the technical validity and comparability between methods for measuring leachable proteins make skin testing with glove pieces a nonstandardized procedure. It cannot be recommended as routine practice in the clinical setting. A large-scale comparison of the predictive value of these techniques for the presence of clinical allergy in exposed health care workers is needed urgently.

Alternatively, low affinity cross-reactivity with pollen antigens and fruit antigens [14] may allow cross-reactive positivity in sensitive *in vitro* methods, especially in atopic individuals.

There was no association between type I symptoms and any method of testing for latex-specific IgE, a method which simply shows that a subject can produce IgE specific for (or cross-reactive with) an allergen present in the test preparation. Since different latex allergens may contain different allergens, an extract prepared from one source may not be reactive in individual patients who are sensitized to other products [15]. This may explain why one volunteer was found positive on all the *in vitro* methods but negative on SPT. A subject may be sensitized to proteins in latex products that are not found in raw latex [16,17]. The affinity and avidity of an individual's IgE molecules for latex proteins may also vary, and the concentration of blood borne latex-specific IgE does not predict the severity of an allergic reaction [18].

Standardized extracts and International Reference Preparations for validation of methods for *in vitro* and *in vivo* testing are urgently required.

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