

Latex allergy and skin

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Purpose of review

In this review we address the prevalence and outcome of latex allergy in health care workers (HCWs). Recent findings in natural rubber latex (NRL) allergens and trials of specific immunotherapy (SIT) are also of interest.

Recent findings

A study involving skin prick test (SPT) screening in HCWs in Russia and adjacent countries found a prevalence of latex allergy of 1.9%. Questionnaire studies performed in Wales and in the USA identified prevalence rates of about 0.6%. An intervention undertaken at the Mayo Clinic, in which only gloves with low or undetectable allergen levels were allowed, reduced markedly the incidence of NRL allergy. Two studies, one from Finland and another from Ohio, showed that outcomes in latex-allergic HCWs are generally good. A study involving SPT screening showed that 6% of construction workers had latex allergy. A questionnaire study among allergists practicing in the USA showed that 62% performed latex SPT and 6% reported anaphylaxis, which mostly occurred while using a homemade SPT solution. Hev b 2, Hev b 5, Hev b 6.01 and Hev b 13 produced positive SPT reactions in over 60% of latex-allergic individuals. Topical application of NRL in a murine model of protein contact dermatitis caused a striking increase in prohevein-specific (Hev b 6.01) immunoglobulin E levels, together with a T-helper-2 type dermatitis. A placebo-controlled SIT trial with NRL extract alleviated cutaneous symptoms but caused some systemic reactions in latex-allergic patients.

Summary

Low prevalence rates suggest that the peak of the latex allergy epidemic has already passed in HCWs. Hospital-wide interventions requiring use of low-allergen gloves reduce sensitization and changing gloves to nonlatex ones, or even using low-allergen latex gloves, in the affected individuals appears to confer adequate secondary prevention. In the USA there is an urgent need for standardized latex SPT reagent. Hev b 5 and Hev b 6.01 are major *in vivo* NRL allergens. Findings in mice suggest that NRL proteins eluting from latex gloves may also cause hand eczema in humans. SIT with NRL extract must still be considered an experimental treatment.

Keywords

health care workers, immunotherapy, latex allergy, outcome, skin prick test

Abbreviations

HCW	health care workers
NRL	natural rubber latex
PCD	protein contact dermatitis
SIT	specific immunotherapy
SPT	skin prick test

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Introduction

Latex allergy has been an important health issue for almost two decades. It has been recognized as a major source of occupational contact urticaria, rhinitis and asthma among health care workers (HCWs) [1]. Previous studies based on skin prick tests (SPTs) indicate that 2–17% of exposed HCWs are sensitized to natural rubber latex (NRL) [2,3]. Thirteen different NRL allergens have been characterized at the molecular level, as recently reviewed by Yeang [4]. Hevein (Hev b 6.02) and Hev b 5 are major allergens in latex gloves and are important sensitizers [5,6]. Reliable methods with which to measure allergen content in gloves are now available [6–8]. Glove use policy has changed toward powder-free gloves, and low allergen content is the goal [9]. Hospital-wide interventions aimed at controlling the amount of NRL allergen exposure are needed to reduce sensitization rate and allow latex-allergic HCWs to continue their work [10,11]. Of special interest are trials of specific immunotherapy (SIT) in latex-allergic individuals [12].

An important supplement entitled ‘Natural rubber latex sensitivity’ appeared in the *Journal of Allergy and Clinical Immunology* in August 2002 [13]. Several review articles on latex allergy [14–16] and a UK position paper [17•] have also been published.

Prevalence of latex allergy

Previous studies based on SPT screening have shown that 2–17% of exposed HCWs are sensitized to NRL whereas the rate in general population is less than 1% [1–3]. The prevalence of latex allergy is lower because some sensitized individuals are asymptomatic.

Health care workers

In agreement with previous prevalence studies based on SPT screening, a recent Brazilian study conducted in 96 HCWs in a neonatal intensive care unit [18] found that 8% were sensitized and 5% had clinical latex allergy. A large prevalence study was conducted in Russia and eastern Europe by Nolte *et al.* [19] who used SPT to screen 901 HCWs. Forty-nine (5.4%) HCWs in 15

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collaborating hospitals were sensitized, and 17 (1.9%) were classified as having latex allergy based on the presence of clinical symptoms and a positive SPT. The most frequently reported latex-related symptom was contact urticaria (45%), contact dermatitis (25%) and angio-oedema (20%). The authors concluded that the prevalence of NRL allergy in Russia and adjacent countries is considerably less than reported in HCWs exposed to NRL in western European countries and the USA. An accompanying editorial [20] pointed out some shortcomings of the study (i.e. the study population was not stratified by occupation or extent of glove use). Of interest is that, in these Russian and eastern European hospitals, latex gloves are frequently reused after washing, which would be expected to remove residual latex allergens from the gloves.

Very low prevalence rates of latex allergy in HCWs were found in two recent questionnaire-based screening studies conducted in Wales and in the USA. The prevalence of latex allergy was 0.56% in the study performed by Chowdhury and Statham [21] in 4439 HCWs employed in a national health system trust in Wales. A total of 3716 (67%) HCWs responded and 257 were clinically suspected of having latex allergy and were further investigated. Twenty-five HCWs (9.7%), 18 of whom were nurses, were confirmed as having latex allergy by SPT or latex radioallergosorbent test, or both. Zeiss *et al.* [22*] assessed the prevalence of latex allergy in the personnel of three Department of Veterans Affairs medical centres in Wisconsin and Illinois using a detailed questionnaire and latex CAP assay, but no SPT was performed. Of 1959 individuals, 133 (6.8%) had allergic symptoms from the gloves but only 11 (8%) had positive latex CAP assay, possibly because of the rather low sensitivity of this assay. Thus, confirmed latex allergy was also infrequent in this cohort, occurring in only 0.6% of the 1959 employees. One reason for the low latex allergy prevalence could be that almost a half of the individuals included in the cohort had no or only low exposure to the gloves. The results of the studies from Russia, Wales and the USA emphasize the importance of confirming clinical suspicion of NRL allergy with an objective measure of immunoglobulin E sensitization. On the other hand, questionnaire-based screening studies focused only on the HCWs with apparent symptoms from gloves fail to identify those sensitized individuals who, once a glove use test has been performed, are found to have clinical latex allergy.

Construction workers

Increased occurrence of latex allergy in glove-using occupations other than HCWs is well documented [1,17,23]. A study performed by Conde-Salazar *et al.* [24] added construction workers to the list of such occupations. A prospective SPT screening study in an

occupational dermatology clinic identified 16 (7%) construction workers who were sensitized to NRL and 14 (6%) of them presented with contact urticaria. The authors pointed out that the use of latex gloves in these workers is frequent and the quality of gloves far from standardized. If this high sensitization rate were to be confirmed in another extensive study, then a recommendation that construction workers be systematically screened for NRL allergy would be justified.

Chronic urticaria

Generalized urticaria is among the systemic symptoms of latex allergy. Piskin *et al.* [25] examined whether latex allergy could be an aetiological factor in chronic urticaria. Fifty patients were examined with latex SPT and CAP assay, and the results compared with those in 50 healthy control individuals. Two (4%) patients with chronic urticaria and none of the healthy control individuals exhibited a positive SPT, whereas CAP assay was positive in six (12%) patients and six control individuals. The authors concluded that the frequency of sensitization to NRL in chronic urticaria is not higher than that in healthy individuals. Nucera *et al.* [26] described two latex-allergic individuals who presented with chronic urticaria, which improved when the patients started to avoid foods that crossreact with NRL. The authors did not, however, mention which foods were avoided and whether the patients had positive SPT to avocado or other cross-reactive fruits.

Outcome of latex allergy in health care workers

Prospective studies on the incidence of latex allergy in HCWs after interventions are of the utmost importance. Use of latex gloves with high allergen content is a risk for cutaneous sensitization and production of allergic symptoms in already sensitized HCWs [9]. When powdered or powder-free high-allergen latex gloves are used in hospitals, the levels of air-borne NRL allergens can be high, which is a significant risk factor for latex-induced asthma [27,28]. An important intervention has been undertaken since 1993 at the Mayo Clinic, in which only gloves with low or undetectable allergen levels are allowed to enter the work environment. Hunt *et al.* [29] reported that this intervention reduced the incidence rate of latex allergy from 0.15% to 0.027%. At the same time there was a dramatic reduction in reports of work-related symptoms in the medical records of 187 latex-allergic HCWs, and there were no new reports of change of work area.

Two other studies, one from Finland and one from the USA, provided more detailed data and confirmed that the outcomes of latex-allergic HCWs are generally good. For a mean of 3 years, Turjanmaa *et al.* [30] followed up 71 latex-allergic HCWs who had exhibited symptoms

ranging from contact urticaria (79%) to anaphylaxis (5%). Ten latex-allergic HCWs switched to nonlatex gloves and the other 61 individuals and their co-workers continued to use low-allergenic powdered gloves. None of HCWs exhibited work-related cutaneous or respiratory symptoms, and they all were able to continue in their work. A similarly good outcome was reported by Bernstein *et al.* [31•] in Ohio. Work-related symptoms resolved in 44 (90%) HCWs who switched to nonlatex gloves and remained in their current workplace. Of the 11 HCWs who presented exclusively with contact urticaria and changed to nonlatex gloves, all had complete resolution of work-related hives. Eighteen HCWs with contact urticaria and work-related rhinitis made a glove change, and 15 (83%) remained symptom free. The three HCWs with symptoms reported persistent rhinitis but no contact urticaria. Only four (17%) HCWs with work-related asthma were compelled to change employment to a latex-free workplace, resulting in a mean 24% reduction in annual income.

Several studies have found an association between hand eczema and presence of latex allergy in HCWs [19,32]. In 71 HCWs, Turjanmaa *et al.* [30] found that the hand eczema rate reduced from 54% to 38% ($P=0.02$) following avoidance of high-allergen gloves. Outcome of hand eczema can thus be good in some HCWs, but whether eczema in these individuals is a manifestation of protein contact dermatitis (PCD) or type IV cell-mediated allergy from NRL proteins [33] needs to be investigated.

Skin prick testing and latex allergens

Commercial SPT reagents are available in Europe and Canada but not in the USA. In-vitro assays possess suboptimal diagnostic sensitivity as compared with SPT in identifying HCWs with latex allergy [34]. A questionnaire study conducted by Farrell *et al.* [35] examined diagnostic procedures for latex allergy among 519 allergists practicing in the USA. The majority (64%) used radioallergosorbent test as a first diagnostic test. SPT was performed by 62% of the allergists, and a majority (72%) used solutions made from gloves. The majority (88.7%) used SPT in five or fewer patients per month. Twenty-seven (6%) allergists reported anaphylaxis occurring in patients undergoing latex allergy testing. Most of these episodes occurred while using a homemade prick test solution. It is therefore evident that allergists practicing in the USA urgently need standardized, Food and Drug Administration approved SPT reagents.

Thirteen proteins in NRL that bind human immunoglobulin E *in vitro* have been characterized at the molecular level and are termed Hev b allergens (www.allergen.org). How these proteins elicit cutaneous reactions in sensitized people is not fully understood.

Bernstein *et al.* [36•] examined in-vivo reactivity of seven native and one recombinant (Hev b 5) NRL allergens with SPT in 62 latex-allergic HCWs. Four NRL allergens, namely Hev b 2, Hev b 5, Hev b 6.01 and Hev b 13 (a recently identified NRL allergen), produced SPT reactions in 63–65% of HCWs and were considered major in-vivo NRL allergens.

There is agreement that Hev b 6.02, Hev b 5, Hev b 3 and Hev b 1 and are the principal allergens detectable in latex gloves [5,6]. Yeang [4] recently reviewed the significance of the currently recognized NRL allergens and concluded that Hev b 2, Hev b 6 and Hev b 13 are the major allergens to which latex-sensitized adults react. However, the role of Hev b 2 and Hev b 13 is controversial. Although native Hev b 2 and Hev b 13 seemed to be adequately purified from NRL in the study conducted by Bernstein *et al.* [36•], we could show that similar Hev b 2 and Hev b 13 allergen preparations reacted with monoclonal anti-Hev b 6.02 antibodies [37]. Minute amounts of immunoreactive Hev b 6 in allergen preparations could explain the high prevalence figures, and therefore the significance of Hev b 2 and Hev b 13 as putatively important NRL allergens awaits confirmatory studies.

Effects of natural rubber latex in a murine model of protein contact dermatitis

Hand eczema is a frequent finding in latex-allergic HCWs and other latex glove users [23,30,32]. Eczema can disappear during latex avoidance, suggesting that at least in some individuals eczema could be a manifestation of PCD or a type IV reaction to NRL proteins [30,33].

Lehto *et al.* [38••] examined the effect of repeated topical application of NRL in a murine model of PCD. In this model, a slight mechanical injury to the skin is induced by tape stripping, which makes the skin more susceptible to antigen penetration and induces upregulation of several cytokines, which in turn enhance activation of Langerhans' cells and favour the development of T-helper-2-type immune response [39]. After tape stripping, patches containing 100 µg NRL in phosphate-buffered saline or placebo were placed on the skin for 7 days and then removed. This application was repeated twice with 2-week intervals, after which the mice were killed. Evaluation of biopsy specimens from NRL-sensitized skin sites revealed marked epidermal thickening associated with an inflammatory response characterized by influx of eosinophils and CD3⁺ and CD4⁺ cells. The number of degranulated mast cells was also significantly increased. The sensitized skin sites showed also markedly increased mRNA expression of IL-1β, IL-4 and chemokines CC chemokine ligand-4 and -3. Reflecting a systemic

response, a striking increase in total and prohevein specific (Hev b 6.01) but not in Hev b 1 specific immunoglobulin E levels was found. These findings suggests that cutaneous sensitization to NRL proteins eluting from latex gloves can, in addition to the production of high levels of NRL-specific immunoglobulin E antibodies, contribute to the development of hand eczema. The availability of this model system facilitates the investigation of the molecular and cellular mechanisms of NRL protein induced skin inflammation. Moreover, efficacy of novel therapies for NRL protein induced skin inflammation can be tested in this murine model.

Immunotherapy and anti-immunoglobulin E treatment of latex allergy

SIT with well-characterized and potent mixtures of relevant allergens is a potential option for treatment of latex allergy [12]. Sastre *et al.* [40•] investigated the usefulness of a standardized NRL extract in 24 latex-allergic patients with established latex allergy (eight patients with contact urticaria and 16 with rhinitis or asthma) in a double-blind placebo-controlled SIT study lasting 6 months. Clinical efficacy presented mainly as alleviation of cutaneous symptoms, although improvements in rhinitis and asthma were also observed. Systemic reactions were encountered in 8% of doses, which is less than in certain earlier studies. However, the occurrence of systemic reactions indicates that this kind of treatment must still be considered experimental and needs to be administered in a hospital setting. In the SIT study conducted by Pereira *et al.* [41] four latex-allergic patients, all with histories of severe systemic reactions to NRL, were treated with NRL extract for a period up to 5 years. The mean SPT wheal diameter to NRL decreased but the change was not statistically significant. One patient experienced a systemic reaction.

Because crude NRL extracts tend to cause systemic reactions in SIT, Karisola *et al.* [42•] designed and developed 'hypoallergenic' hevein (Hev b 6.02) molecules. Hevein was subjected to site-directed mutagenesis at six amino acids located in previously determined conformational immunoglobulin E binding B-cell epitopes [43]. Immunoglobulin E binding affinity of the mutated molecule decreased by several orders *in vitro*, and four latex-allergic patients, who had clear-cut SPT reactions to natural hevein, exhibited no reactivity to the mutated molecule. This strategy of modifying immunoglobulin E binding conformational epitopes may be valuable when developing 'hypoallergenic' molecules for SIT in latex and other important allergies.

Leynadier *et al.* [44] investigated the effect of omalizumab in a placebo-controlled, double-blind study conducted in latex-allergic HCWs. Nine HCWs received

anti-immunoglobulin E and nine received placebo therapy, given as subcutaneous injections every 2 or 4 weeks for 16 weeks. Efficacy was primarily monitored by conjunctival challenges, but SPTs and glove use tests were also performed at the end of the study. A clinically relevant decrease in ocular scores was found in the omalizumab group. Tolerability was good, with only two reported injection-site reactions.

Conclusion

The evidence based on screening studies suggests that the height of the latex allergy epidemics in health care has already passed. One of the problems in combating latex allergy has been the difficulty in standardizing the quality of latex gloves. Recent developments in methods for measurement of NRL allergen content in gloves have made possible interventions with the use of low-allergen latex gloves. This approach seems to be the best way to achieve primary prevention of latex sensitization and allergy in a hospital setting. Reviewed studies also show that the clinical outcome of latex-allergic HCWs is generally good in a workplace where only low-allergen gloves are used. Despite of the progress made in the primary and secondary prevention of latex allergy in health care, much work remains to be done in this field and especially in other occupations that require the use of gloves.

NRL proteins eluting from latex gloves sensitize people, and there is agreement that the major allergens present in gloves are hevein (Hev b 6.02) and Hev b 5. A study with SPT confirmed that these same proteins are the major *in vivo* allergens in HCWs. The reviewed SIT trials with crude NRL extract showed that the need for more efficient and safer SIT allergens remains. Good animal models are invaluable for examining sensitization to NRL and performing trials with putative allergen molecules for SIT. The results from a murine model of PCD showing a strong prohevein-specific immunoglobulin E response is of special interest with regard to the cutaneous sensitization route. The observed T-helper 2-dominated dermal inflammation with eczematous skin reaction could be one mechanism by which NRL proteins cause hand eczema in latex-allergic HCWs.

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