

Natural rubber latex allergy and asthma

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Allergic responses to natural rubber latex (NRL) continue to be reported. In adults, the major exposure is in the occupational setting, especially in relation to NRL glove use by health care workers. Issues addressed over the past year include improving diagnostic methods for NRL allergy and characterization of NRL allergens relevant to various exposure groups and evaluating strategies for prevention and early detection of NRL allergy. Assessment of *in vitro* tests show good intertest correlation but lower sensitivity compared with skin test responses. NRL allergens have been further characterized as reported in the past year. Development of recombinant Hev b 3, a major NRL allergen relevant to children with spina bifida, enhances the likelihood for improved diagnostic reagents. Preliminary reports of primary preventive strategies suggest that avoidance of high-protein, powdered gloves in health care facilities can be cost-effective and is associated with a decline in sensitized workers. *Curr Opin Pulm Med* 2001, 7:27–31 © 2001 Lippincott

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Abbreviations

NRL natural rubber latex

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Allergic, IgE antibody-mediated responses to natural rubber latex (NRL) proteins were first described in Europe by Nutter [1] in 1979. Since then there have been an increasing number of reports of IgE-mediated NRL allergy, manifest most commonly as contact urticaria or angioedema and most often related to NRL glove usage, as well reviewed by Vandenplas *et al.* [2]. Sensitized individuals may also develop symptoms of allergic rhinitis, conjunctivitis, or asthma from exposure to airborne NRL proteins, generally from local use of powdered NRL gloves. Anaphylactic responses can also occur, usually from NRL contact with mucosal or serosal membranes in sensitized individuals, during surgery, dental or medical procedures, or from NRL glove contact with disrupted skin, as in sensitized individuals with hand eczema who use NRL gloves.

The risk factors for NRL sensitization have been well described. Most sensitized individuals have a history of frequent NRL contact; in adults, occupational use of NRL gloves (such as health care workers, dental hygienists, or hairdressers) and manufacture of NRL products (such as gloves, dolls, condoms, or textiles) are the most common sources of sensitization. A history of frequent surgical procedures with NRL contact is another risk factor for sensitization, especially for children with spina bifida (29–72% have been reported to be sensitized) [3] and children with congenital urologic abnormalities requiring frequent catheterization. It is now recommended that such children avoid NRL contact from birth. Other risk factors include atopy, food allergy, and disrupted skin contact with NRL products.

Similarly, there have been several reports on the prevalence of NRL allergy in health care workers (range, 5–17%) and other occupationally exposed groups, as recently reviewed [2]. Prevalence studies reported in the past year for hairdressers in Finland, health care workers in England, and workers in a glove plant in Turkey have suggested lower prevalence rates than in earlier studies [4–6]. It is difficult to determine whether this is due to differences in diagnostic methods compared with earlier studies or perhaps to lower NRL allergen exposure in these groups as compared with groups previously reported.

Over the past year, many of the published studies relating to NRL allergy and asthma have focused on three unresolved issues: improving diagnostic methods for NRL allergy, improving the characterization of NRL

allergens relevant to various exposure groups, and evaluating strategies for prevention and early detection of NRL allergy.

Diagnostic methods for natural rubber latex allergy

At the current time diagnostic skin tests preparations of NRL are commercially available in Europe and Canada. However, in the United States, only *in vitro* tests have been cleared by the US Food and Drug Administration for use. In a blinded, multicenter evaluation of the CAP (Pharmacia-Upjohn, Kalamazoo, MI) and AlaSTAT (Diagnostic Products, Los Angeles, CA) assays for serum IgE antibodies to NRL, Ownby *et al.* [7] have compared the results with history and skin prick test results using ammoniated or nonammoniated NRL extracts.

In vitro assays were performed on sera from 83 NRL-allergic individuals (history and skin test positive) and 60 non-NRL-allergic individuals. Twenty-six percent of the NRL-allergic patients had spina bifida. Both *in vitro* test results were similar, with sensitivity 80 and 75% for CAP and AlaSTAT, respectively, and specificity 90 and 92%, respectively. These findings are similar to results previously found by Hamilton *et al.* [8], who compared the same *in vitro* tests with skin prick test results, also mainly in an adult population. These earlier results showed higher specificity for the *in vitro* tests (97% for each) as compared with the more recent study. These findings are similar to comparisons of the *in vitro* tests with skin prick tests using other allergens, again emphasizing the need for available NRL skin prick test extracts for greater sensitivity of NRL diagnosis.

A high rate of sensitization to NRL has been previously well documented in patients with spina bifida. Differences have been identified in the specificities of IgE antibodies to NRL allergens between these patients and those with occupationally induced NRL allergy. This has led to an attempt to characterize and produce recombinant NRL allergens relevant to spina bifida patients. Wagner *et al.* [9••] have cloned and expressed Hev b 3 allergen. The recombinant Hev b 3 was produced in *Escherichia coli* and characterized by immunoblotting and inhibition assays. It was able to abolish all IgE binding to native Hev b 3, and in immunoblots 83% of 35 NRL-allergic spina bifida patients (confirmed by NRL glove challenge) had IgE binding to the recombinant Hev b 3. In contrast, the NRL skin prick test using a commercial extract (Stallergènes, Fresnes, France) was positive in only 51% of these NRL-allergic patients with spina bifida. These findings suggest a better sensitivity of *in vitro* testing with a recombinant NRL allergen in spina bifida patients, in contrast to the results with commercial *in*

vitro tests in other (predominantly occupationally sensitized) NRL-allergic patients.

Glove “use tests,” involving the application of a piece of NRL glove directly onto wetted skin, have been used as a method of challenge testing for diagnosis of NRL allergy. These have been used as a gold standard of diagnosis in patients who have a positive history but negative skin prick tests or *in vitro* tests for NRL allergy [10]. However, as recently reported from the same Finnish group [11], several brands of NRL glove can contain cow’s milk casein, which could cause contact urticaria in those with cow’s milk allergy [12], falsely suggesting NRL allergy, and false-positive skin prick tests could occur in such patients if glove eluates rather than NRL extracts are used for skin testing.

Inhalation challenge tests in the workplace or laboratory, with exposure of the patient to powdered latex gloves with monitoring of pulmonary function, have been used for diagnosis of NRL-related asthma. However, there have been fewer reports of nasal challenges with NRL or other occupational allergens. Raulf-Heimsoth *et al.* [13] have assessed nasal lavage cytology and mediators after powdered glove challenges in sensitized health care workers, and Palczynski *et al.* [14] used similar measures after instillation into the nose of an NRL glove eluate. As might be expected, both studies demonstrated an increase in nasal lavage eosinophils and mediators such as eosinophil cationic protein (ECP) in NRL-allergic health care workers with NRL-related nasal symptoms. These studies were not associated with systemic anaphylactic responses. However, the study that used whole-glove challenge [13] did provoke an asthmatic response requiring bronchodilator treatment in five of the subgroup of 10 subjects challenged who had both rhinitis and occupational asthma from NRL. These findings suggest, as might be expected, that when challenges are needed for objective documentation of rhinitis, local nasal challenge is likely to be safest, but if objective confirmation of NRL-related asthma is also required, then exposure to powdered NRL gloves is likely to be more sensitive.

Characterization of natural rubber latex allergens

The ability to better characterize NRL allergens may lead to better skin test and *in vitro* diagnostic preparations; better understanding of cross-reactivity with other allergens, particularly from foods; and the possibility of assessing feasibility of immunotherapy for NRL-allergic patients. Among approximately 240 polypeptides in NRL, nearly 60 have been reported to be antigenic and at least nine have been registered by the World Health Organization International Union of Immunological Societies’ Allergen Nomenclature Subcommittee. The

others continue to be investigated, as recently reviewed by Petsonk [15] (Table I). Proportional concentrations of different antigens can vary 25- to 100-fold between different lots of NRL materials and can relate to stress on the rubber trees (*Hevea brasiliensis*), season of the harvest, duration of storage, chemicals added to the NRL solution, and heating of the product [16–18]. Hännine *et al.* [19••] have shown that treating turnips with salicylic acid or an ethylene-releasing agent (both of which act as stressors to the plant) will increase the content of a proheveinlike defense protein that cross-reacts with NRL prohevein allergen and many other proheveinlike defense proteins. These findings illustrate not only the cross-reactivity of some allergens between different plant species but also the potential increase in plant allergenicity that may occur with agricultural interventions that may increase plant stress. This might be relevant to the apparent development and increase of NRL allergy in the late 1980s and early 1990s, when the increased demand for NRL gloves may have been associated with increased tapping of NRL from the rubber trees (*H. brasiliensis*) and increased stress on the trees.

Identified NRL allergens, to date, include proteins that appear to have a role in the rubber trees, in wound healing and inhibiting fungal growth (1,3- β -glucanase [Hev b 6.02]), storage proteins, as well as structural proteins (as reviewed by Petsonk [15]). Some have homology to proteins in several fruits and vegetables, likely accounting for some of the clinical association of NRL allergy with food allergy, especially allergy to banana, kiwi, avocado, mango, and chestnut [20,21].

In assessing the association with food allergy, Posch *et al.* [22•] have previously reported that 61% of 38 NRL-allergic health care workers showed positive skin tests to avocado. Recently [23] they have shown that the major

cross-reacting allergen causing allergic responses to avocado in NRL-allergic health care workers is a class I endochitinase containing a hevein domain cross-reacting with the hevein domain of the major NRL allergy prohevein (Hev b 6.01). IgE antibodies directed against this 31-kD allergen were detected by immunoblotting in 80% of avocado-sensitized NRL-allergic patients. Levy *et al.* [24] have also confirmed the association of NRL allergy with food allergy to avocado and banana, in contrast to patients with pollenosis, who demonstrated an association with allergy to apple, peach, and celery. Because NRL allergy is more common in atopic individuals, sensitization to NRL and to pollen with concurrent food allergy associations may coexist. In addition, Merrett *et al.* [25] demonstrated allergenic cross-reactivity of some serum IgE with both grass pollen and NRL, with a greater percentage of blood donors demonstrating NRL IgE antibodies during the grass pollen season when specific IgE antibodies to grass pollen are highest (7%), as compared with the winter months (4%).

Management, prevention, and early detection of natural rubber latex allergy

It has been recognized that NRL allergen exposure can be reduced by changing to powder-free, low-protein NRL gloves in occupations in which NRL gloves are required. However, the limited data available suggest that only a minority of hospitals have changed to powder-free or non-NRL gloves [26], despite US government statements to support this approach from the National Institute for Health and Safety (NIOSH) [27], the Centers for Disease Control [28], and the Occupational Safety and Health Administration [29].

The US Food and Drug Administration has also proposed a reduction in NRL glove powder and protein content [30]. A cost-benefit analysis by Phillips *et al.* [31] indicated that in health care facilities there is a cost-

Table 1. Latex allergens registered by the World Health Organization International Union of Immunological Societies' Allergen Nomenclature Subcommittee

Allergen	Source	Molecular weight, kD	Function
Hev b 1	Rubber particle	14.6	Rubber elongation factor. Has homology to Hev b 3. Interacts with isoprene to form isoprene polymers.
Hev b 3	Rubber particle	23–27.0	Homology to Hev b 1. Both are important in sensitized spina bifida children.
Hev b 2	Soluble	34–41.3	Endo-1,3- β -glucanidase. Homology to enzymes from many plant species.
Hev b 4	Soluble	50–75.0	Microhelix protein.
Hev b 5	Soluble	16.0	Unknown function. IgE antibodies to this are present in 92% of sensitized health care workers, less in spina bifida patients.
Hev b 6.01	Soluble	20.0	Prohevein. Defense protein, also in other plants [23] as an endochitinase, can be induced in plants by chemical treatment [9••]. A common allergen in adult NRL-sensitized patients but less in spina bifida.
Hev b 6.02	Soluble	4.7	Hevein, lysozyme/chitinase with homology to other plant defense proteins. Derived from prohevein.
Hev b 7	Soluble	46.0	Patatin, storage protein. Homologous with other plant patatins.
Hev b 8	Soluble	14.0	Profilin, an actin-binding protein, homologous to other plant profilins.
Hev b 9	Soluble	51.0	Enolase.

NRL, natural rubber latex. Data from [15].

benefit to a change to nonlatex gloves even if, without a change in gloves, 1% or less of those at risk were to become fully disabled and 2% or less were to become partially disabled from NRL allergy. Allmers *et al.* [32] previously showed that a change to powder-free or synthetic gloves, in a health care setting, resulted in a decrease in measurable airborne NRL allergen within 24 hours. The seven among 90 workers in this study who had been previously sensitized to NRL allergens had a significant decrease in specific IgE antibody levels to NRL over the following year, and the two with asthma symptoms were able to discontinue medication.

Early reports in abstract format suggest that this strategy may also decrease the prevalence of NRL allergy among hospital employees, in Finland [33] and in Canada [34,35], but full papers detailing the outcomes of such strategies in preventing NRL allergy have not as yet been published.

Current management of NRL sensitivity consists of preventive measures and appropriate medication for allergic manifestations. There is only anecdotal published evidence to date of the possible effectiveness of specific immunotherapy, *eg*, as described by Pereira *et al.* [36] in one patient, apparently with benefit. Further understanding of relevant NRL allergens, with development of these, may in the future permit specific therapy to be an option for health care workers who may continue to have difficulty avoiding NRL products.

Conclusions

Major developments have been made in the past year in characterizing NRL allergens and developing recombinant allergens. Future development in this area may lead to improved diagnostic methods and possibly therapeutic agents for sensitized patients. However, there remains a major need for primary preventive measures, and further published studies are needed to evaluate the effectiveness of various preventive measures, particularly in health care settings.

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