

# Natural rubber latex allergy after 12 years: Recommendations and perspectives

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Natural rubber latex (NRL) allergy is a “new” illness whose prevalence reached epidemic proportions in highly exposed populations during the last decade. In children with spina bifida and in patients exposed to NRL during radiologic procedures, institution of prophylactic safety measures has had demonstrable effects in preventing allergic reactions. The risk of NRL allergy appears to be largely linked to occupational exposure, and NRL-associated occupational asthma is due almost solely to powdered latex glove use. Prevalence of NRL-allergic sensitization in the general population is quite low; several studies of young adults demonstrate rates of positive skin test results that are less than 1%. After occupational exposure, rates of sensitization and NRL-induced asthma rise dramatically in individuals using powdered NRL gloves but not in individuals using powder-free gloves. Airborne NRL is dependent on the use of powdered NRL gloves; conversion to non-NRL or nonpowdered NRL substitutes results in predictable rapid disappearance of detectable levels of aeroallergen. For these reasons, adoption of the following institutional policies designed to prevent new cases of NRL allergy and maximize safety is recommended: (1) NRL gloves should be used only as mandated by accepted Standard Precautions; (2) only nonpowdered, nonsterile NRL gloves should be used; and (3) nonpowdered, sterile NRL gloves are preferred for use. Low-protein powdered, sterile gloves may be used, but only in conjunction with an ongoing assessment for development of allergic reactions. (*J Allergy Clin Immunol* 2002;109:31-4.)

**Key words:** Latex, natural rubber latex, occupation asthma, allergic sensitization, latex gloves, Standard Precautions

For much of the modern medical era, natural rubber latex (NRL) was viewed as an innocuous and relatively immunologically inert material. Its virtues—notably, strength, flexibility, elasticity, and comfort—all proved attractive in a variety of applications and medical devices. Untoward reactions to NRL gloves were thought

## Abbreviations used

NRL: Natural rubber latex

SPT: Skin prick testing

to be limited to contact dermatitis caused either by non-specific irritation or, less frequently, by type IV sensitization to chemical additives. The attractive properties of NRL, combined with superior barrier qualities and tear resistance, led to its widespread use as a convenient and cost-effective way of limiting the spread of transmissible diseases such as HIV and hepatitis C. An estimated twenty-plus billion pairs of gloves were sold in the United States alone last year.<sup>1</sup>

Accordingly, reports of anaphylactic events in children with spina bifida<sup>2</sup> and of fatal anaphylaxis associated with the use of NRL barium enema retention<sup>3</sup> were greeted initially with consternation and even disbelief. At this time, however, there is common agreement about the nature of these IgE-mediated type I allergic reactions to NRL proteins.<sup>4-6</sup> Furthermore, institution of prophylactic safety measures has been effective at preventing further problems in these populations. Although the risks of NRL allergy are now well appreciated by most clinicians and scientists in this field, some controversy still attends both the degree and the nature of risk of latex allergy among those working with powdered and nonpowdered latex gloves as well as in the general population.

Working with data collected from the Third National Health and Nutrition Examination Survey, some industry-sponsored papers have suggested that allergic NRL sensitization is common (estimated at 18%) in the general population.<sup>7,8</sup> These reports both question the existence of NRL allergy as an occupational illness and challenge proposals to limit the use of powdered latex gloves. However, these studies rely on a serologic test for which the specificity is at best only 95%.<sup>9,10</sup> As a consequence, when the test is used for screening in low-prevalence populations, the true prevalence rates might be significantly overestimated.<sup>11</sup> We believe that there is sufficient evidence to conclude that NRL allergy increases with occupational exposure; furthermore, we believe that NRL-associated occupational asthma is due almost solely to the continued use of powdered latex gloves.

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As with other allergic responses, development of clinically relevant allergic symptoms remains dependent on exposure to allergen, and the risk of NRL allergy increases in those who are atopic. For example, in children with spina bifida, early and frequent exposure increases the rates of both allergic sensitization and clinical allergic reactions,<sup>12</sup> and rates of NRL sensitization commonly exceed 25% on skin prick testing (SPT).<sup>2,13,14</sup> In contrast, children with spina bifida without extensive exposure histories demonstrate a much lower rate of sensitization and clinical allergy,<sup>15</sup> and NRL sensitization is uncommon in the general pediatric population.<sup>16</sup>

Similarly, the prevalence of NRL sensitization in adults increases with occupational exposure, as shown in multiple studies using sensitive and specific SPT techniques.<sup>9,17,18</sup> Extensive studies using the Bencard reagent in Canada,<sup>19,20</sup> a glove extract in Finland,<sup>21,22</sup> and Staller-genes reagent in France<sup>12,23</sup> have yielded consistent findings of an approximate 1% rate of sensitization in the general population and a rate of between 1% and 9% in the atopic population. In both groups, clinical allergic reactions were rare. In contrast, among those with occupational latex exposure, SPT results with these same reagents were positive in 5% to 12% of subjects tested, and approximately half of these individuals reported histories of allergic symptoms.<sup>20,22,24-27</sup> Of even greater concern is the fact that several studies report a 2% to 10% prevalence of occupational asthma in highly exposed workers.<sup>26,28,29</sup>

Studies investigating the effect of increased latex exposure on those entering the workplace are especially relevant to an understanding of the epidemiology of occupational disease because they avoid the problem of only healthy individuals remaining in the study population (survivor bias). Three such studies have been published.<sup>30-32</sup> In all of these studies, less than 1% of entry apprentices and dental students had positive SPT results, which is consistent with the findings noted in non-occupationally exposed subjects cited above. In a cross-sectional investigation, Tarlo et al<sup>30</sup> observed that concurrent rates of sensitization were 6% in tested third-year students, 10% in fourth-year students, and 25% in faculty members at the University of Toronto. In a separate cross-sectional study, Levy et al<sup>31</sup> reported that graduating dental students in Paris and London demonstrated positive SPT results in 15% and 5%, respectively, of students using powdered gloves but that none of the students who used powder-free latex gloves was allergic—a statistically significant difference. Last, a prospective study of 769 apprentice animal health, pastry-maker, and dental hygiene workers by Gautrin et al<sup>33</sup> demonstrated that the 6% prevalence rate of latex sensitization was significantly higher in the dental hygiene group than in the other groups as a result of more prolonged exposure to latex gloves.

As distinguished from other acute IgE-mediated allergic reactions, NRL-induced asthma develops as a response to chronic respiratory exposure to latex aeroallergens that generate airway sensitization and inflammatory responses characteristic of allergic asthma. Among latex-allergic individuals sensitized as patients, reports of

NRL asthma are exceedingly rare. In contrast, the condition is not rare in those with occupational exposure. Specific inhalation challenges in workers with histories of asthma confirm an asthmatic response to glove allergens in the vast majority of affected workers. Perhaps more worrisome, acute airway obstruction could be induced during inhalation challenge with NRL allergens in nearly one half of those without asthma but with a documented positive skin test response to NRL.<sup>34</sup>

Latex aeroallergen, measured in a variety of medical settings, is dependent on the use of powdered NRL gloves, but after conversion to exclusive use of nonpowdered latex and nonlatex gloves, levels fall rapidly. The relevance of these findings to the pathogenesis of occupational asthma is bolstered by the report of Baur et al,<sup>35</sup> who calculated a statistical threshold level of aeroallergen that is associated with an increased prevalence of sensitization and symptoms. Use of cornstarch-powdered latex gloves, which are currently available, is associated with an unacceptable risk of occupational disease in glove-wearers. Furthermore, recent demonstration of passive dispersion of latex aerosol in a health care facility suggests that use of powdered latex gloves carries both risk to other workers and significant risk of inadvertent exposure to NRL-sensitive patients.<sup>36</sup>

On the basis of these data, we endorse most of the recommendations made in the 1997 statement of the American College of Allergy, Asthma & Immunology<sup>37</sup>—with slight modifications, associated with the realization that there are differences between allergen exposure from sterile NRL and allergen exposure from nonsterile NRL.<sup>38,39</sup> These recommendations are also tempered by our recognition that data on allergen levels for procured gloves are not readily available to purchasers. For these reasons, we recommend that the following policies be implemented at this time to both minimize the number of new cases of latex allergy and maximize the safety of those workers and patients already clinically allergic:

- Use of latex gloves should be restricted; they should be used only as mandated by accepted Standard Precautions protocols. To further reduce exposure and cost, routine use of latex gloves by individuals not exposed to contaminated fluids (ie, in low-risk situations), such as food-handlers and transport personnel, is strongly discouraged.
- Only nonpowdered, nonsterile NRL gloves (ie, examination gloves) should be used (ie, <2 mg donning powder per glove).
- Powder-free sterile NRL gloves are preferred for use. Because sterile NRL gloves appear to cause only infrequent problems in nonallergic individuals, use of low-protein powdered surgical gloves (<50 µg/g ASTM D5712) rather than nonpowdered gloves is acceptable if an ongoing assessment for development of allergic reactions is maintained.

During the 12 years of this epidemic, much clinical and scientific knowledge has been acquired. The major risk groups and factors predisposing for latex allergy have been identified. Clinical manifestations have been charac-

terized, and increased awareness and institutional policies have prevented most potentially life-threatening reactions. Scientific efforts resulted in the cloning and expression of 11 allergens with promise for improved diagnostic potential. Nonlatex medical devices and protocols for dealing with latex-allergic patients are available in many health care institutions. Progressive substitution of powder-free latex gloves or synthetic alternatives for powdered latex gloves is ongoing.<sup>1</sup> However, considerable work still lies ahead, at least in part because of the significant variability in NRL allergen content between different glove batches and different glove brands. Some other relevant issues include the following:

1. Information about the natural history of latex allergy is scant. The proportion of asymptomatic patients with latex sensitivity that progresses to clinical reactivity is unknown. Outcomes from the utilization of strict avoidance measures remain unclear, including whether and at what rate allergic sensitization diminishes or disappears.
2. The relationship between aeroallergen levels and clinical symptoms or long-term asthmatic progression requires further study. Large longitudinal follow-up studies focusing on the course of latex occupational asthma are needed.
3. Further intervention studies would be useful to determine the cost-effectiveness of prevention measures, both primary (general measures of exposure reduction) and secondary (eg, early identification of sensitized individuals). Such investigations should also focus on the clinical consequences of active interventions on latex exposure and its potential cost-savings.
4. The diagnosis of latex allergy is problematic in the United States, where no US Food and Drug Administration-licensed skin test reagent is available. In vitro tests for latex IgE show relatively low sensitivity, and false negative results are frequent (~25%). In addition, cross-reactivity with pollens and plant food allergens can lead to both specific and nonspecific binding to carbohydrates.<sup>40-42</sup> The development of standardized or recombinant latex allergen test reagents might increase testing accuracy.
5. Adverse reactions to latex-associated plant foods are frequent and potentially severe. From a diagnostic perspective, it is not always clear whether latex sensitization precedes or follows the onset of food allergy, but its presence might compromise accurate diagnosis of this condition. Study of latex-pollen and latex-food cross-reactions could hasten development of in vitro assays, which have better diagnostic performance.
6. Preliminary results of latex-specific immunotherapy have been reported,<sup>43</sup> but further standardization of immunotherapy extracts and clinical trials with larger numbers of sensitive persons will be required before this approach can be made widely available. The possibility of individualized immunotherapy dependent on specific patterns of allergen recognition, as well as the possibility of DNA vaccines, is an exciting new area of investigation.
7. The problem of latex avoidance is complicated by the occasional finding of extractable latex allergen in synthetic gloves.<sup>44</sup> Further refinements in glove manufacturing methods might yield significant decreases in the allergenicity of latex gloves and have the additional benefit of reducing cross-contamination of non-NRL gloves with NRL allergens in production facilities where both types of gloves are produced.

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