

Natural Rubber Latex Sensitivity Seminar: Conference summary

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Latex allergy presents major medical, legal, and public policy problems, yet there is surprisingly little consensus on the fundamental issues that comprise its core. The purpose of the current conference is to distinguish knowledge from conjecture and identify areas that need strengthening so that appropriate guidelines for management and prevention can be developed.

Natural rubber is a processed product derived from latex, the sap of the rubber tree, *Hevea brasiliensis*. Latex is composed of spherical polyisoprene droplets coated with a layer of water-soluble proteins. Once gathered, *Hevea* sap is converted into liquid latex concentrate and solid dry rubber. The former is used to make a variety of items such as gloves, condoms, balloons, catheters, baby pacifiers, and dental dams, and the latter serves as the essential ingredient in tires, tubing, hoses, footwear, automotive components, engineering parts, and adhesives. The latex concentrate contains about 1% total protein, a small fraction of which remains in the product as residual extractable proteins (EPs). This is the material that binds to specific human IgE antibody and has been implicated in allergic reactions. In contrast, dry rubber contains very little protein and therefore is much less immunogenic.

Allergic reactions to virtually all forms of latex products have been reported, but natural rubber latex (NRL) gloves are associated with the greatest prevalence in the hospital setting. Gloves are the principal barrier against transmission of viral and bacterial pathogens from body fluids between health care providers and patients and serve to protect both. After the "universal precautions" recommendation was made by the Centers for Disease Control in the late 1980s, the demand for gloves increased dramatically, resulting in an acute shortage. As manufacturers struggled to meet demands, products of variable quality began to appear in the marketplace, and the magnitude of the allergy problem grew. Gloves of this early

Abbreviations used

EPs: Extractable proteins
NRL: Natural rubber latex

era had a wide range of EP content, depending on manufacturing procedures. It was soon apparent that the EPs can produce sensitization on contact with various areas of the body and that the dusting powder on the gloves could facilitate the process. High EP levels are invariably associated with positive skin prick test responses, whereas low levels tend to demonstrate reduced allergenic reactions. If the quantities of EPs are held to ≤ 100 $\mu\text{g/g}$, the allergenicity falls to zero. On the basis of this recognition, concerted efforts have been made to reduce the protein content of latex products; and new manufacturing technologies, such as the use of low-protein substrates, prolonged leaching, and chemical and enzymatic deproteinization, are in place. In addition, attempts to deal with the powder on the gloves have been made.

In the early days, standard practice was to dip gloves into modified cornstarch slurries during processing to facilitate easy donning and keep the sides from sticking together. Proteins attach to the cornstarch and then can become widely disseminated antigens when the particles of powder become airborne as the gloves are donned and removed. It is now appreciated that the allergen content of the glove powder derives from the protein concentration of the slurry tank at the time of the powdering application and is not related to the allergen content of the glove on which the powder is applied. Thus, the allergen content can be reduced by frequently changing the bath. It can also be modified by changing the type of starch used. Dusting powder particles do absorb glove proteins, but the amounts of such transfers are very small, and the lower the EP content, the lower is the ultimate antigenicity. Similarly, it is the protein content of the powder, not the amount of the powder, that is the primary concern. In gloves with low EP content, the antigenicity of the powder becomes negligible. Therefore, powdered gloves need not be a serious allergy issue with proper manufacturing.

Powder-free gloves obviate many of the previously mentioned problems, but they create unique ones of their own. The chlorination process used in their manufacture reduces the tack of the rubber and allows the glove to be used without the need for a powder lubricant; however, this treatment is not sufficient to allow the gloves to be donned when the user's hands are wet or damp. For this purpose, a polymeric coating is required.

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The most important criterion for the selection of gloves for safe use should be their ability to prevent the passage of microbes to and from the skin of the wearer. Properly manufactured NRL gloves are known for their excellent barrier property, high strength, good elasticity, tactile sensitivity, comfort, fit, and durability. Synthetic gloves still do not have all of these properties. Low-protein, low-powder, and low-protein powder-free NRL gloves are now produced to prevent or minimize further sensitization among users. For latex-sensitive individuals, the gloves of choice should be those made of protein-free synthetic materials because the best treatment is to avoid the allergens to which they are responsive. Furthermore, it is important to point out that synthetic gloves, particularly vinyl gloves, have poor barrier performance, and although they may be protein-free, they are not allergen-free. Incidences of type IV allergy caused by residual chemicals, and even type I hypersensitivity, have been reported.

Data from the Centers for Disease Control and Prevention National Surveillance System for Hospital Health-care Workers clearly delineate the epidemiology of exposure to blood and other potentially infectious materials in the workplace and the magnitude of the risk workers continue to face. Most exposures occur in inpatient wards (30%), operating and procedure rooms (29%), intensive care units (14%), and emergency and outpatient departments (15% combined). Rates of exposure in central processing areas and laboratories are lower but still important. Not surprisingly, nurses (44%) and physicians (30%) are at greatest risk. Gloves generally do not prevent needle puncture, although they may reduce the volume of blood reaching the skin, nor do they prevent injury during surgery. Needles from syringes (34%), sutures (16%), butterflies (13%), and scalpels (7%) remain the most frequent causes of percutaneous injuries. The hollow-bore needles used during phlebotomy tend to pose the greatest risk (25%). Other procedures such as intramuscular or subcutaneous injections (19%), insertion of intravascular catheters (14%), and manipulation of an intravascular line (14%) are somewhat less problematic.

Rubber gloves of one type or another have been in use for most of the preceding century. Although contact dermatitis was recognized early on, the first anaphylactic reaction to surgical gloves was not described until 1984. By the mid to late 1980s, reports of systemic reactions began to appear, and the first study of the prevalence of immediate-type allergic sensitivity to latex in hospital employees was published. The first case of occupational asthma soon followed, and by the end of the decade, latex-related anaphylaxis in children who had multiple operations was described. It soon became apparent that the common denominator for sensitization and allergy was frequent exposure to NRL products, and high-risk groups began to be identified. Health care workers, children with spina bifida (and other individuals undergoing multiple surgeries), atopic subjects, and persons working in industries that collect and process latex and manufacture products that contain it are particularly vulnerable.

The possible relationship between latex and food allergy was first reported in 1989.

The functional and structural characteristics of latex proteins have come under increased scrutiny, and molecular biologic techniques have been used to standardize the allergens. Work is being carried out to improve the accuracy, sensitivity, reproducibility, and practicality of current and new assays. Important proteins include those involved in the biosynthesis of polyisoprene and coagulation of latex rubber elongation factor, small rubber particle protein, prohevein, and patatin. Pathogenesis-related proteins include β -1-3-glucanases, chitinases, and heveamine; whereas the structural proteins include microhelix protein complex, proline-rich protein, profilins, enolases, and magnesium superoxide dismutase. Overall, NRL contains more than 200 proteins. Ten of these (the *H brasiliensis* proteins) bind IgE and have been recognized by the International Union of Immunological Societies as being relevant to latex allergy. Recombinant allergens are reactive on skin prick testing and can be produced in a standardized manner to provide safe and sensitive reagents for diagnosis and treatment. Recombinant allergens and the components of the analytic reagents are undergoing testing to determine their clinical utility.

It is critical to remember that the diagnosis of latex allergy always needs to be confirmed objectively. This is best accomplished with an algorithm that begins with a comprehensive clinical history that assesses risk factors such as atopy, food allergies, hand dermatitis, and the temporal relationship between symptoms and natural rubber product exposure. If type IV hypersensitivity is a potential issue, patch testing can be conducted to confirm the presence of activated T cells with specificity for rubber chemicals. If type I hypersensitivity is suspected, confirmatory skin or blood tests for IgE antibody may be conducted to verify the state of sensitization. A definitive diagnosis requires both an affirmative history and independent positive laboratory test results. In vivo provocation tests such as placing individuals in latex-containing environments or having them don and remove gloves or using a hooded exposure chamber can be performed when latex-specific serology and/or skin test results are discordant with the clinical findings.

Exposure to latex proteins can occur through a number of ports of entry including intact skin, the eyes, the gut, and the upper and lower respiratory tracts. Particle size is not an important consideration with the first 4 routes, but it is for the intrathoracic airways. It is not yet clear whether local contact of the allergen with the integument or conjunctiva can produce symptoms in other organs. High-risk populations are described above, but the quantities of allergen necessary to initiate IgE production are unknown and cannot be deduced from currently available data. One study has suggested that sufficient exposure to latex in health care workers can lead to increased sensitization, but other investigations are less clear and the matter remains controversial.

Anaphylactic reactions to latex during surgical and medical procedures are a great fear but, fortunately, are

uncommon. The prevalence of anaphylaxis during such circumstances has been stated to vary from 1 in 5000 to 1 in 10,000 cases, and latex allergy accounts for only 10% to 17%. The populations at risk for the latter include persons with a genetic predisposition such as atopy and those with increased previous exposure to latex (eg, multiple surgeries, long-term bladder care, repeated insertion of latex catheters, or long-term use of indwelling catheters). For reasons that are unclear, latex anaphylaxis occurs most commonly during obstetric and gynecologic procedures.

From 3% to 17% of health care workers are said to have latex allergies, and their long-term prognosis is not yet established. Data on the effect of changing the type of gloves used in a working environment to low-allergen latex or nonlatex products in a group of sensitive health care and non-health care workers indicate favorable results. Three years after such a change, no person with latex sensitization or allergy had to change jobs, and there was a significant decrease in symptoms. Hence, it appears that reducing antigen levels in gloves works well, even for individuals with established problems.

Latex EP-induced nasal, eye, and lower airway complaints are pressing problems that have generated a great deal of research activity as indicated in the literature; however, because of the lack of large prospective studies, very little is known for certain about the incidence or natural history of such illness. Most information concerning the prevalence of rhinoconjunctivitis and asthma is derived from cross-sectional studies assessing sensitivity and self-reported symptoms in exposed health care workers. Unfortunately, such data are often confounded by methodological issues for skin and serologic testing, differences in the levels of exposure of the populations studied, and the unreliability of self-reported symptoms on questionnaires. Nonetheless, by combining the data from large studies, it is possible to come to an "order of magnitude" assessment of the prevalences of sensitization, per se, and of prevalences of these specific illnesses, in particular. With this approach, the pooled rate of sensitization to latex in health care workers is around 8%, and the pooled rates for rhinoconjunctivitis and asthma are 7.8% and 1.4%, respectively. These are not particularly large effects compared with other forms of exposure. For example, contact with laboratory animal dander causes skin test sensitization in 13% of workers, rhinoconjunctivitis in 18.7%, and asthma in 7.4%. In addition, the prevalence of occupational asthma caused by chemicals such as toluene diisocyanate and plicatic acid approaches 19%. Finally, the risk of subsequent development of asthma in animal workers with rhinoconjunctivitis approaches 40% in contrast to a 20% risk in those with latex-derived nasal-ophthalmologic complaints. The reasons for these differences are not yet established but may be due to poorer penetration of the latex allergens. Irrespective of mechanism, the new forms of glove manufacturing and patterns of glove use are expected to diminish further the frequency of NRL-induced occupational respiratory disease.

In conjunction with the previously mentioned analysis, epidemiologic data also support the notion that the role of latex gloves in causing sensitization and allergic symptoms remains poorly defined because of inconsistent results among studies. Such studies do not support a conclusion that health care workers are at increased risk for latex sensitization or allergies compared with persons in other occupations in the United States. The data in the literature estimate the incidence of latex sensitization among health care workers to be between 1% and 2.5% per year as determined by skin testing. Increased risk is not clearly associated with the duration of work in health care, the time spent wearing latex gloves, the frequency of exposure, the specific job categories, the use of powdered versus nonpowdered latex gloves, the use of latex versus nonlatex gloves, or any measures of ambient exposure to latex proteins.

Policies that include institution-wide intervention measures aimed at controlling the amount of latex allergen protein exposure are essential for reducing the number of workers who become sensitized, as well as for controlling or eliminating complaints in those who are allergic. Systematic evaluation of instituted strategies shows a dramatic decrease in new cases, a reduction in the number of workers presenting with symptoms, and an absence of employee transfers because of uncontrolled medically related latex issues. Methodical approaches that examine all features of the problem permit the appreciation and identification of unexpected confounding factors. One particularly troubling confounding factor is "latex-associated pseudoallergy syndrome," in which patients experience repeated attacks of choking with upper chest tightness, loss of voice, facial pruritus, cough, and dyspnea, even though they do not have any objective evidence of hypersensitivity.

Latex-sensitive individuals are advised to minimize their exposure to this allergen as a matter of course, but limited data exist as to the relative effectiveness of the various techniques in current practice. Provision of a completely latex-free environment in the surgical suite may be unrealistic, but much can be done when institutions approach the problem with multidisciplinary input to establish environmental control and develop policies and procedures for identifying and caring for health care workers and patients with allergies. In surgical and medical settings, much of the allergen that is shed into the air comes from donning and removing gloves. In one hospital system, antigen concentrations in areas of heavy glove use ranged from 14 to 122 ng/m³ and from undetectable to 2 ng/m³ in locations of minimal glove use. The quantities of allergen in the personal breathing zone varied with the number of gloves changed and ranged up to 1000 ng/m³. After adoption of a latex allergen control policy, repeated measurements at these sites were consistently below 10 ng/m³ and usually below 1 ng/m³. Data from controlled exposure challenges suggest that levels <10 ng/m³ do not elicit symptoms. A controlled study in operating suites confirmed the efficacy of using low-allergen powdered gloves. Because the powder particles are relatively large, they settle out of the air rapidly. Two

thirds of the airborne allergens are carried on particles $>14\text{ }\mu\text{m}$, and only about 20% are carried on respirable particles, so concentrations do not reach threshold levels. In a companion study, the use of a laminar flow glove changing station did not reduce antigen levels, but environmental control measures that substituted synthetic or powder-free gloves for powdered NRL gloves significantly reduced aeroallergen levels and prevented or reduced symptoms in sensitive individuals.

It is estimated that 40,000 consumer products contain NRL and are capable of sensitizing humans. More noteworthy is the fact that latex allergens are ubiquitous and can be detected in foods, spices, pollen, and plants; thus, exposure outside of a medical setting is significant and can develop from contact with multiple sources of cross-reacting proteins. Interactions may also occur. Immediate hypersensitivity reactions have been reported as a result of contact with items such as condoms, balloons, baby bottle nipples, rubber dental dams, toys, and sports equipment. In some instances, these reactions have been amplified or initiated by cross-sensitization to foods, whereas in others, contact with latex EPs appears to have worsened food allergies. These phenomena are important in that patients sensitive to foods containing latex allergens need to be advised of the possibility of developing reactions to the myriad of products containing NRL and those with allergies to latex should be made aware of the risks of certain foods.

A 5-point stepwise approach for administratively managing high-risk health care workers with NRL allergy has been proposed. The algorithm recommends confirming the diagnosis of NRL allergy by using rational, validated methods; presenting medical justification for cessation of further exposure in the workplace; determining that total temporary disability resulting from NRL allergy exists; advising employers and risk managers regarding the diagnosis and the responsibility to institute effective environmental interventions; and finally, if accommodation efforts are unsuccessful, advising the employee to seek workers' compensation benefits and eventual rehabilitation. Because objective evidence of residual impairment caused by NRL-induced anaphylaxis or occupational asthma is often absent, the physician must determine disability on the basis of how work restrictions resulting from such allergy affect the worker's ability to perform his or her current duties. Injury ratings must be repeated every 6 months for the first 2 years. According

to the Americans with Disabilities Act, an employee with latex allergy and no objective evidence of impairment would not be considered to have a disability after EP exposure and the risk of work-related asthma and/or anaphylaxis have been eliminated.

In 1995, a latex allergy case incurred costs of \$220,000 within the first year of the claim. After the institution of directed protocols, the average cost of latex-related claims and the impact of them on the lives of health care workers were reduced substantially through objective evaluation of the physiologic response in the workplace. The critical elements are believed to be early intervention by an experienced disability management nurse and a physician with skills in diagnosing latex sensitivity, familiarity with the subtleties involved in interpreting objective test results, and experience in disability management. As alluded to elsewhere in this summary, dealing with latex claims presents many challenges including misdiagnosis, psychologic factors, information gaps, ineffective controls, limited knowledge, and future employment issues. As protocol approaches are more rigorously applied, expertise in dealing with each of these areas increases.

The explosion of latex sensitivity has fostered a need to develop means of evaluating and controlling potential contact. Based on the chemical and physical characteristics of latex allergen particles, reliable, accurate, and precise analytic methods have been developed. Although dose-response relationships of airborne concentrations to measurable biologic responses have not been elucidated, reasonable exposure criteria are available. A low-risk environment (ie, concentrations of latex in the air $<10\text{ ng/m}^3$ and dust contamination $<10\text{ }\mu\text{g/g}$) should preclude provocation of an allergic response. A moderate risk level (air concentrations of $10\text{--}50\text{ ng/m}^3$; dust concentrations of $10\text{--}100\text{ }\mu\text{g/g}$) could cause a reaction in sensitized individuals, whereas a "high" level has values above 50 ng/m^3 in the air and $100\text{ }\mu\text{g/g}$ in dust. "High" risk levels are defined as likely to cause an allergic reaction in latex-sensitive individuals but are not high enough to produce initial sensitization. Control of latex exposure can ultimately be accomplished by removing products that contain these substances from the workplace and substituting nonlatex items in their stead, using local exhaust ventilation, enclosing the work area, and/or using personal protection in the forms of skin coverings and respirators.