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Review

Latex allergy: past and present

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Abstract

Although latex products have been in use for over a century, allergic responses to latex proteins have only been recognized as a serious health problem for the past 15 years. Latex allergy particularly affects two groups, health care workers (HCW) and children with spina bifida (SB). This manuscript provides a brief history of latex allergy, and a review of the following: the manufacturing process for dipped latex products, the 11 latex allergens that have been characterized and received allergen designations by the International Union of Immunological Societies, the methods used in exposure assessment, the epidemiology and clinical management of latex allergy, and the use of animal models in investigating mechanisms underlying latex allergy. © 2002 Published by Elsevier Science B.V.

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1. Introduction

Latex allergy has received worldwide attention during the last decade. Several factors make latex allergy unique. Latex products were in use for over a century prior to the diagnosis of latex allergy in epidemic proportions. Unlike many IgE-mediated allergies, which are induced by a single or few major allergens, there are hundreds of proteins in latex products, with 11 allergens having been identified, each bearing numerous epitopes. Also, two distinct populations are particularly affected by latex allergy, health care workers (HCW) and children with spina bifida (SB) or other conditions requiring multiple surgeries early in life. Interestingly, these two populations appear to have sero-reactivity to different individual latex protein profiles. The severity of allergic reactions to latex proteins is another distinguishing factor, as anaphylaxis has been unusually common among latex-allergic individuals. Although information is available regarding the routes and, to some extent, the levels of exposure required to elicit clinical symptoms in allergic individuals, less is understood about the amount of protein and time required or the relevance of the route of exposure during the development of sensitization.

1.1. History of latex usage and adverse responses to latex products

The first widespread use of latex products in the medical field was in the production of dentures. In 1851, the denture manufacturing process perfected by Charles Goodyear was patented [1]. One of the first cases of urticaria to latex was a reaction to a dental plate that was reported in 1927 [2]. With the invention of the vulcanization process, the use of latex became wide-

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spread, resulting in its use in the manufacture of over 40,000 products today. Halstead first introduced the use of latex surgical gloves in 1896 and the first reported case of contact urticaria to latex household gloves was described in 1979 [3]. A year later, Forstrom [4] reported contact urticaria caused by surgical gloves. It was not until 1986 that it was determined that the reactions to latex products were IgE-mediated [5] and that the allergens were latex proteins contaminating the products [6].

Between 1989 and 1992, there were over 1100 cases of allergic responses to latex products and 15 deaths resulting from latex protein-induced anaphylaxis reported to the US FDA [7]. An additional 1200 allergic reactions and 13 deaths had been reported by 1997, (Gawchik S. ''The Role of Organizations,'' the 1998 National Latex Allergy Conference, San Antonio, TX, US). Over 9.9 million people are employed by the health care industry in the US [8], and of these, 2.9–12.1% are estimated to be latex-allergic. Additionally, approximately 1% of the general population may be sensitized to latex [9]. Although the reasons underlying the increase in latex allergy are unknown, it has been suggested that several factors are involved. Subsequent to the issuance of ''Universal Precautions'' in 1987, there was a tremendous increase in glove use in the US. Use increased from fewer than 1 billion pairs per year to over 20 billion pairs of gloves in 1996 [10]. This increase in demand for gloves resulted in changes in latex harvesting and manufacturing practices that may have altered the protein content and allergenicity of the gloves.

Adverse responses to latex products fall into three major categories; irritant contact dermatitis (ICD), allergic contact dermatitis (ACD), and IgE-mediated responses, and there is an inverse relationship between prevalence and severity. Most responses are irritant dermatitis that do not require prior exposure and do not involve immunological memory. Most irritant responses have been attributed to friction between the glove and occluded skin and to the donning powder, which is often alkaline [11]. Numerous chemicals are added to latex during manufacturing and many are irritants and/or sensitizers. Examples of these chemicals are shown in Table 1. The second most frequent adverse reaction is allergic contact dermatitis, a T cell-mediated hypersensitivity response. Many chemicals used as accelerators and vulcanizing agents in the manufacturing process are contact sensitizers (Table 1). Although irritant and allergic contact dermatitis are not life-threatening, they cause significant morbidity and reduced work performance. Irritant and allergic contact dermatitis disrupt the skin barrier and alter the normal physiology of the skin, which may lead to development of the more serious, but less frequent, IgE-mediated responses to latex proteins [12–14]. The role of chemicals in IgE-mediated responses to latex products is not known, but it has been postulated that some may function as haptens.

Table 1
Chemical irritants and sensitizers used in the manufacture of NRL gloves

Chemical	Irritant	Sensitizer	Reference
Ammonium hydroxide	yes	[a]	MSDS
Formaldehyde	yes	yes	[105–108]
Tetramethylthiuram disulfide (TMTD)	[a]	yes	[106,109,110]
Zinc oxide	yes	[a]	MSDS
Sodium laurel sulfate	yes	yes	[106,108,111,112]
Thiuram mix	[a]	yes	[110,113]
Carbamates	[a]	yes	[110,113]
Mercapto compounds	[a]	yes	[110,113]
Diphenylamine	no	yes	[114,108,110]
Phenylene diamine	weak	yes	[108,114]
Amines	yes	yes	[106,113]
Phenol	yes	no	[106,111]
Black rubber mix	[a]	yes	[110]
Naphtyl mix	[a]	yes	[110]

[a] Literature not found.

1.2. Manufacture of dipped latex products

Processing of natural rubber latex (NRL) involves harvesting, anti-coagulation, concentration, and compounding. NRL is harvested from *Hevea brasiliensis* trees, primarily in Southeast Asia. A cytoplasmic exudate of the lacticifer layer, NRL contains 30–45% rubber, cytosolic organelles, nucleic acids, and proteins typically found in plant cells. Keeping the latex liquid is essential for the manufacture of ''dipped'' rubber products (gloves, condoms, catheters, balloons, etc.). Only 10–20% of rubber is tapped for latex, the remainder coagulates at the tree and is processed into dry rubber for products such as tires, hoses, belts, and gaskets [15].

At tapping, chemicals such as ammonium hydroxide, formaldehyde, tetramethylthiuram disulfide (TM-

TD), and zinc oxide are added to prevent coagulation of the rubber and to inhibit bacterial or fungal growth [16]. The raw latex is centrifuged to concentrate the rubber to approximately 60%. Prior to manufacturing, the latex is formulated (compounded) by the addition of surfactants (Darvan, laurel sulfate), sulfur compounds (colloidal sulfur), Zn oxide, accelerators (thiurams, carbamates, and/or mercapto compounds), anti-oxidants and anti-ozonants (diphenylamine, phenylene–diamine, phenols), and other chemicals [17].

Dipped latex products are produced in assembly line fashion. Product shaped molds are immersed in tanks of coagulant (calcium nitrate) to coat the formers and then dipped in the compounded latex (dipping) to produce a thin coating of latex on the surface of the mold. The device can then be leached while the latex is still moist (pre-vulcanized leaching), passed through ovens (vulcanization), and leached post-vulcanization, before the addition of lubricants (powders or polymers). Vulcanization is a key step that produces the cross-linking of the isoprene molecules resulting in an effective elastomeric barrier. Donning powder (cornstarch), when used to facilitate donning and removal of gloves, is added by dipping the gloves into a powder slurry. Alternatively, powder-free gloves undergo a chlorination process to de-tactify the film, allowing glove donning.

1.3. Effects of manufacturing on residual allergens

Treatment of field latex with ammonia to prevent coagulation causes the latex proteins to hydrolyze. The hydrolyzed peptides and chemicals bloom to the surface during the drying and vulcanization stages. Once on the surface, most of the residuals can be removed by leaching. The coagulants and other chemicals are leached out of the wet gel films during pre-vulcanization leaching. But as long as moisture remains in the wet gels, protein can continue to migrate to the surface of the film. Thus, in order to be effective in protein reduction, leaching must also be done post-vulcanization and drying.

Special consideration must be given to the slurry tanks for powder application, as they appear to be the major source of problems. As gloves are dipped into the slurry (typically 10% cornstarch), residual proteins and chemicals leach from the film. As millions of gloves are dipped into the slurry, proteins accumulate and reach a high concentration [18]. When the slurry dries onto the gloves, accumulated proteins then dry back onto the surface of the glove and the powder. When dry, the powder acts as a carrier for the residuals (proteins and chemicals) and becomes airborne during donning and removal of gloves. Accumulation of proteins in the slurry tanks also promotes the growth of bacteria, leading to high levels of endotoxin in the tanks and subsequently on the gloves. Replacement of the powder slurry with the chlorination step to produce powder-free gloves drastically reduces the protein content and endotoxin levels of the gloves [19,20].

2. Characterization of latex allergens

When analyzed by 2-D electrophoresis, non-ammoniated latex (NAL) contains more than 250 peptides [21]. Currently, 11 NRL proteins have been cloned, sequenced, expressed as recombinant proteins, and given allergen designations. The allergens found in latex include proteins involved in the biosynthesis or coagulation of polyisoprene (Hev b 1, 3, 6), pathogenesis related proteins (Hev b 2, 6, 7, 11), structural proteins (Hev b 4, 5, 8), and housekeeping enzymes (Hev b 9, 10). There is considerable heterogeneity in individual reactivity to specific latex proteins [22] and there appears to be preferential reactivity to certain proteins among different patient populations. For example, Hev b 1 and 3 are more common allergens for patients with medical exposure, such as SB or other urogenital malformations [23], while other proteins (Hev b 5, 6, 7) are more common allergens for HCW with occupational exposures [24].

Hev b 1 is a 14.6-kDa protein that is found tightly bound to rubber particles and is thought to facilitate the elongation of the isoprene chains. Hev b 1 was the first protein to be identified as an allergen in latex [25]. The protein is characterized, cloned, and sequenced, and both B cell and T cell epitopes have been identified [26]. Hev b 1 has at least two major IgE epitopes with sequence homology and limited cross-reactivity to papain from papaya [27].

Hev b 2 is a 65-kDa β 1–3 glucanase, one of a family of enzymes that catalyze the hydrolytic cleavage of polymers of β 1–3 glucans. Glucans are major components in the cell wall of fungi, so these proteins help to defend plants against fungal infection. Hev b 2 is glycosylated and some of the reported differences in

reactivity to Hev b 2 [24,28] appear to be due to anti-carbohydrate antibodies recognizing the native but not the recombinant Hev b 2.

Hev b 3 has been isolated, cloned, and characterized as a small rubber particle-bound protein [29] involved in the biosynthesis of isoprene. Originally identified as a 27-kDa [30] or 23-kDa [31] allergen, this 22.4-kDa protein has significant sequence homology with Hev b 1 [32]. While Hev b 1 and 3 proteins may share B cell epitopes, they appear to have unique T cell epitopes [33]. Hev b 1 and 3 have increased reactivity in SB patients in comparison to HCW, suggesting the potential for genetic factors or route of exposure to influence the IgE response to latex.

Hev b 4 is a protein of approximately 50 kDa isolated from the lutoid fraction [34]. The *N*-terminal amino acid sequence appears unique, however, the protein has not been cloned and little is known about it. The protein appears to be part of a protein complex that forms spring-like micro-helices with unknown function and appears more abundantly in latex after Ethrel stimulation [16].

Hev b 5 is a glutamic acid and proline-rich protein with homology to proteins in kiwi, potato, and sugar beet. The function of the protein in latex is unknown but some of its features suggest that it may be a structural protein. Hev b 5 was isolated by cloning the cDNA [35,36]. The protein has a predicted mass of 16 kDa but runs at 36–100 kDa in gels and is heat-stable [35]. Hev b 5 is a potent allergen for HCW and SB patients and contains at least six epitopes [37,38]. Two major T cell epitopes have been identified, and recently, hypoallergenic mutants of the protein with immunotherapy potential have been produced by recombinant technology [39,40].

Hev b 6 is probably the most studied allergen in latex. Prohevein is synthesized as a 20-kDa protein (Hev b 6.01) but cleaved into a 5-kDa hevein (Hev b 6.02) and a 14-kDa C-Domain (Hev b 6.03). Hevein binds to chitin, a protein found in the cell walls of fungi and insects, and thus serves as a defense-related protein. The C-domain (Hev b 6.03) has homologies to wound-inducible proteins [41]. First identified as an allergen by sequence analysis of IgE reactive protein bands [22], subsequent studies found the *N*-terminal hevein (6.02) to have most of the clinical reactivity [42]. Epitope studies identified at least six B cell epitopes [41]. The epitopes are in regions of homology to hevein-like proteins and class I chitinases, which are widely distributed in plants.

Hev b 7 was identified as a 43-kDa protein with structural homology to a potato protein called patatin. Patatins are storage proteins but also have phospholipase activities and defense functions in plants. The protein has been cloned and characterized [43,44] and multiple isoforms have been identified with similar IgE reactivities. Allergy to potato, banana or avocado among latex-allergic HCW could not be linked to the cross-reactivity of Hev b 7 [45].

Hev b 8 was identified as a member of the profilin family, a well-known pan-allergen. Profilins are actin-binding structural proteins known to be involved in celery–mugwort–spice syndrome. Profilin from latex has been cloned and sequenced [24,46] and has significant homologies to other profilins [47]. Few latex-allergic adults were found to react to skin testing with rHev b 8 [24].

Hev b 9 is a 47.6-kDa enolase protein identified by cDNA cloning [48]. Enolase is a key enzyme of glycolysis and gluconeogenesis in eukaryotic and prokaryotic cells and has been identified as an allergen from several molds. Cross-reactivity with enolases from molds has not been reported.

Manganese superoxide dismutase is an allergen from *Aspergillus* (Asp f 6) and a 26-kDa homologue has been cloned from *Hevea* latex (Hev b 10). Like Hev b 9, in vitro cross-reactivity can be demonstrated, but clinical cross-reactions between latex and molds have not been reported.

Hev b 11 was recently reported as a 33-kDa type I chitinase [49]. The chitin-binding domain of Hev b 11 has 58% homology with hevein (Hev b 6.02); antibodies to solid phase Hev b 11 could be inhibited 87% by hevein. It appears that the hevein family of proteins (Hev b 6 and 11) are pan-allergens responsible for much of the cross-reactivity of latex with other plant and food allergens [50,51].

3. Exposure assessment

3.1. Testing medical products for latex protein content

It is commonly held that the amount of residual protein on the latex product determines the allergenic potency of the product. Thus, it is necessary to

accurately measure the protein levels of latex products in order to evaluate allergic potential, and subsequently, to choose products with low protein/allergen contents. There are three major approaches to evaluating the amount of protein on rubber products: total protein, antigenic protein, and allergenic protein. Each approach has its merits and its technical problems.

3.1.1. Total protein

Proteins can be routinely measured by relatively simple, chemical methods. These methods rely on the dye-binding properties of certain amino acids but cannot distinguish between allergens, antigens or sources of the protein. Certain compounding chemicals interfere and falsely elevate the readings in the total protein assays [52].

The Lowry method was established as a standardized assay by the American Society of Testing and Materials (ASTM D5712) in 1995. Protein precipitation steps in the procedure reduce interferences, but the method still suffers from interference problems. The US FDA allows manufacturers to make low protein claims if their product contains less than 50 μg/gm by this method. ASTM standards for surgical and exam gloves (D3577 and D3578) recommend <200 μg/dm^2 on all exam and surgical gloves. Currently, the FDA is considering making it a requirement that medical gloves contain less than 200 μg/dm^2 of total protein [53].

3.1.2. Antigen

ELISA methods use animal antibodies to measure antigenic latex proteins. The antigen level is thought to estimate potential allergenic protein content because the immunological processes, whereby proteins are recognized as antigens or allergens, are similar. The antigen assays have been criticized because they use animal sera, however, data indicate that antigenic protein is a useful estimate of allergen content [19,54]. Additionally, ELISAs are not plagued by problems with chemical interferences. Technically, the assays have the advantage of having a common antisera which can be produced and standardized to ensure that the same antigens are being measured by all laboratories performing the assay.

Latex ELISAs have been established in indirect and inhibition formats [19,54,55]. The LEAP assay is an indirect ELISA that has been used by manufacturers since 1993. More recently an inhibition format ELISA has been established as an ASTM standard (D6499-00). Both assays use rabbit anti-ammoniated latex antisera and ammoniated latex (AL) protein as their reference material. D6499-00 reagents are available through the ASTM. The source of protein for the immunization of the rabbits is critical for the ELISA assays [56,57]. Anti-NAL does not perform well for the measurement of protein on latex products because it fails to recognize AL protein on many gloves [56], apparently because of conformational restraints or failure to recognize cryptic epitopes exposed by the ammonia treatment. Currently, ASTM is considering a recommendation of <10 μg/dm^2 of antigenic protein on gloves.

3.1.3. Allergen

The amount of allergenic protein on gloves is determined using IgE inhibition methods. These methods use pooled sera from latex-allergic patients in an inhibition assay format [58–62]. The inhibition format involves a solid phase allergen on disks, tubes, or microtiter plates. A glove extract is mixed with patient sera (latex-specific IgE) and then added to the solid phase allergen. The soluble allergen competes for antibody binding with the solid phase allergen and the resulting inhibition is used to determine the amount of soluble antigen in the samples. Allergen assays have used both NAL and glove proteins as the solid phase with similar results [59]. In testing the allergenicity of product extracts, allergen assay test methods have been found to best correlate with skin prick test (SPT) in latex-allergic patients [19,58], but these methods are difficult to standardize between laboratories because different pools of patient sera are used.

3.2. Assessment of exposure to airborne latex allergens

Inhibition immunoassays have also been applied for assessment of exposures to airborne NRL allergens [60,63]. Reported studies have generally collected total airborne particulate matter by suctioning known volumes of air through filters. Both personal breathing zone and area air samples have been collected, extracted, and evaluated in this manner.

Only a few reports have evaluated the size distribution of aerosolized latex particles. In one report, a

five-stage cascade impactor was used to evaluate the size distribution of NRL allergens in area air samples from a laboratory where technicians were experiencing symptoms of allergy [60]. While 81% of the NRL allergens were reported to be associated with particles of a mass median aerodynamic diameter >7 μm, 13% were associated with smaller particles (<4 μm) capable of penetration into the lower respiratory tract. In another report, airborne particles of glove powder generated by shaking and donning of NRL gloves were examined by electron microscopy [63]; cornstarch particles so generated had diameters mainly in the range of 5–20 μm.

Powdered NRL glove use is a key determinant of airborne NRL allergen levels. Air samples were collected in a single operating room for over 52 consecutive days [64]. During this time, powdered NRL gloves with high allergen contents were used for 18 days, and a mix of powdered and non-powered gloves with low allergen content were used for 10 days, and no surgery was performed during 19 days. NRL aeroallergen levels in the operating room on days of high-allergen glove use were significantly greater than on days of low-allergen glove use or on non-surgical days. On days of high-allergen glove use, NRL aeroallergen levels correlated significantly with the number of gloves used. Aerosols of NRL allergens generated by active use of powdered gloves can also be carried by passive dispersion to areas where gloves are not used, potentially affecting individuals not personally using NRL gloves. NRL allergens can also contaminate upholstery fabric and carpets, which can serve as important repositories for allergens [65].

Where problems related to airborne NRL allergens exist, the use of low protein, powder-free gloves will markedly decrease exposure levels [61,64–66]. The institution of low-protein, powder-free gloves can be justified on clinical grounds, and does not require documentation of airborne NRL allergen levels.

4. Epidemiology

4.1. Considerations affecting assessment for NRL allergy in populations

Epidemiology of NRL allergy, particularly in health care workers, as well as the general population, has been the subject of some controversy [9,67]. Perhaps this is because identification of NRL allergy on a population-wide basis is not straightforward. In the clinical setting, NRL allergy is usually diagnosed based on a compatible clinical history and documentation of IgE-sensitization. Thus, in a population study, documentation of IgE-sensitization without clinical symptoms is not equivalent to identifying clinical NRL allergy.

Another major problem is that tests intended for clinical use may not perform optimally when applied to screening low prevalence populations for a condition such as IgE-sensitization to NRL. Clinical tests are optimized for use in evaluating patient populations where there is usually a high pre-test probability for the condition of interest. Assuming constant sensitivity and specificity, the higher the true prevalence of a condition, the more accurately a test will identify the prevalence of that condition in a population. If a condition is present at low prevalence, a larger proportion of test positives will be false-positives, resulting in poor positive predictive value of the test and overestimation of prevalence [68]. In the case of tests for IgE-sensitization to NRL, the three in vitro tests available for use in the US including (Pharmacia-Upjohn CAP, Diagnostic Products microplate Ala-STAT, and Hycor HY-TEC EIA) have reported specificities of 97%, 97%, and 73%, respectively, relative to SPT [69]. Thus, even if the true prevalence of IgE-sensitization to NRL was zero, these tests would identify 3%, 3%, and 27%, respectively, of a population as being sensitized. Other studies suggest similar performance for serological assays [70]. In contrast, Liss and Sussman [9] reviewed available studies using SPT to estimate the prevalence of NRL sensitization in general population groups and found that estimates from such studies were in the range of 1%.

Another important issue affecting epidemiological studies is that of study design. Most published studies evaluating prevalence and risk factors for NRL allergy are cross-sectional (that is, they evaluate a population at a single point in time). Cross-sectional study design fails to evaluate individuals who have already suffered adverse effects and left the population. Thus, cross-sectional studies can underestimate the prevalence of a condition in an exposed population by failing to evaluate those individuals most susceptible or most exposed. The “healthy worker effect” can prevent a

study from finding relationships between exposure and response and, in the most extreme cases, even result in artifactual findings suggesting that exposures protect against adverse health effects of interest.

4.1.1. NRL allergy in the general population

A number of studies have examined the prevalence of IgE-sensitization to NRL (as opposed to clinical evidence of allergy) in the adult general population [71–73]. A study screening sera from 1000 US blood donors for anti-NRL IgE using the AlaSTAT assay reported a prevalence of positive tests of 6.4% [71]. Another study using three separate laboratories to screen 1997 US blood donors with the AlaSTAT assay reported prevalence rates of positive tests ranging between 5.4% and 7.6% [72]. A study of British blood donors using the AlaSTAT assay found prevalence rates for NRL sensitization of approximately 4% in the winter and 7% in the summer. Cross-reactivity was noted between NRL and grass allergen [73]. These prevalence rates are not much different from the background false-positive rates that would be predicted from the reported specificity of the AlaSTAT assay relative to SPT.

Two European studies have evaluated the prevalence of NRL allergy in all children presented for evaluation in allergy clinics. In one study, 2.2% of 453 children had positive SPT to an NRL extract [74]. Half of the sensitized children reported symptoms related to NRL exposure, mostly triggered by contact with balloons and gloves. In another study [75], 3269 children undergoing allergy evaluations were screened for NRL allergy by SPT with 1.7% positive, and 1.1% confirmed by reexamination. One percent exhibited a combination of positive SPT, RAST and glove challenge.

4.1.2. NRL allergy in children with spina bifida

Children with SB are clearly at increased risk for both NRL sensitization and anaphylactic reactions to NRL during surgery [76,77]. NRL sensitization rates ranging between 34% and 65% have been reported [77–80]. In this population, direct internal and mucosal contact with NRL medical devices may be the route of sensitization, as factors such as number of operations, and use of NRL devices such as catheters or ventriculoperitoneal shunts were associated with increased risk of NRL sensitization and allergy. Atopy has also been documented to be an important risk factor [78–80].

4.1.3. NRL allergy in health care workers

Over the past decade, clinical NRL allergy has been an important occupationally related disease of health care workers [81]. Exposure of latex-sensitized health care workers to NRL can lead to a range of allergic symptoms including contact urticaria, rhinoconjunctivitis, asthma, or even anaphylaxis. Atopic health care workers have consistently been found to be at increased risk for both sensitization and clinical disease [13,63,82–84].

Despite the clear importance of latex allergy as an occupational disease of HCW, the relationship between such employment and IgE-sensitization to NRL has been controversial [9,67]. Some have argued, based on cross-sectional studies evaluating prevalence of IgE-sensitization to NRL, that employment in the health care industry is not a significant risk factor for NRL sensitization [67]. However, as already noted, the prevalence of NRL sensitization in cross-sectional studies of health care workers likely underestimates the role of employment in the development of sensitization because of the healthy worker effect. Furthermore, many of these studies have used serological tests with suboptimal specificities to document IgE-sensitization to NRL. This would be expected to result in high background false-positive rates in control populations, obscuring differences in prevalence of true sensitization between health care workers and the general population [67] or exposed and unexposed health care workers [85].

Despite these issues, several cross-sectional studies have found relationships between employment in the health care industry and IgE-sensitization to NRL. Baur et al. [63,86], in two cross-sectional studies have shown relationships between objective measurements of airborne NRL allergen and risk of sensitization in German health care workers. Levy et al. [87] reported a cross-sectional evaluation of graduating French and English dental students using SPT to evaluate for NRL sensitization. It was reported that students who had used powdered gloves were more likely to be sensitized than students who had used non-powdered gloves.

Cohort studies evaluating the incidence of health effects over time are a preferred study design for

establishing relationships between occupational exposures and health effects, because they are less subject to the healthy worker effect. For studies of allergic sensitization, it is optimal to enroll a cohort of subjects new to the occupational exposure, so that susceptible individuals at risk for early sensitization are included in the study. One such study has been reported examining incidence of specific IgE-sensitization in a cohort of 769 apprentices, including 417 in animal health technology, 230 in pastry-making, and 122 in dental hygiene technology [88]. Subjects were entered into the study within 3 months of the start of exposure to relevant occupational allergens. The dental hygiene students were followed for up to 32 months after the start of routine exposure to NRL. NRL IgE-sensitization was assessed by SPT. The cumulative incidence rate of skin prick test-positivity to NRL over the course of the study was significantly greater in dental hygiene apprentices (7/110) than in pastry makers (3/185; incidence rate ratio IRR) = 3.92, CI = 1.04–14.86) (or animal health technicians (4/391; IRR = 6.22, CI = 1.85–20.86) [89]. Among the dental hygiene students, baseline history of physician diagnosed asthma or respiratory symptoms upon exposure to cold air, as well as atopy defined by SPT using common aeroallergens, were significant risk factors for subsequent incident sensitization to NRL. Sensitized dental hygiene students were significantly more likely to develop incident cutaneous, rhinoconjunctival, and respiratory symptoms (dyspnea and/or wheezing). Cumulative incidence of probable occupational asthma to latex was 4.5% [90]. Thus, current evidence strongly implicates employment in the health care industry as a risk factor for both latex sensitization and latex-induced allergic disease.

5. Clinical management of NRL allergy

5.1. Diagnosis

Diagnosis of NRL allergy is based on the presence of a compatible clinical history and documentation of IgE-sensitization to NRL. A compatible clinical history would consist of symptoms typical of IgE-mediated reactions such as of urticaria, rhinitis, conjunctivitis, asthma, or anaphylaxis in association with exposure to NRL. Documentation of sensitization in the US is generally done using serological testing, as no approved diagnostic extract for use in latex SPT is currently available. Published sensitivities relative to SPT for the three FDA-cleared serological tests range between 73% and 92%, while specificities are between 73% and 97% [69]. In countries where approved allergenic extracts exist, SPT would be the first choice for documentation of sensitization. In some cases, clinical history and tests for IgE-sensitization to NRL give discordant results. In these cases, provocative challenges with NRL allergens can be useful to clearly establish or rule out the diagnosis of NRL allergy [91].

5.2. Treatment

Allergic reactions from NRL exposure should be treated in a conventional fashion. The only current treatment specific to NRL is avoidance of the allergens. Persons afflicted with NRL allergy should not personally use nor undergo procedures using NRL devices such as gloves or catheters. Non-NRL alternatives now exist and should be substituted. Because aerosols generated by the use of powdered NRL gloves can affect bystanders, persons in the vicinity of the affected individual, such as co-workers, should switch from the use of powdered to non-powdered NRL gloves [65]. If problems persist despite these measures, complete elimination of NRL from the affected individual's surroundings must be considered. In the case of health care workers, institution of avoidance measures has allowed workers to continue in their occupations with decreased symptoms, and has been associated with falls in levels of serum anti-NRL IgE [92,93].

A small study of specific allergen immunotherapy for NRL allergy was recently reported [94] in which immunotherapy was associated with symptomatic improvement and decreased sensitivity to conjunctival challenge. However, four of nine actively treated patients experienced a number of significant systemic reactions during therapy. Specific allergen immunotherapy remains an experimental treatment for NRL allergy, and will always be of lesser importance than NRL allergen avoidance. Patients with NRL allergy should be counseled about their condition, especially the risk of anaphylaxis if exposed to NRL during medical procedures, and should wear medical alert bracelets indicating their NRL allergy.

6. Prevention of NRL allergy

In 1997, the National Institute for Occupational Health and Safety issued an alert entitled "Preventing Allergic Reactions to Natural Rubber Latex in the Workplace" [95], in which a variety of measures were recommended to lower exposures to NRL allergens. Substitution of non-powdered, low-protein gloves can lower aeroallergen levels in a medical center, sometimes with little impact on cost [96]. Non-latex devices can be substituted for NRL devices. Administrative controls can be instituted to assure that NRL gloves are used only by individuals truly needing the protection of NRL gloves. Early identification of individuals with NRL allergy might allow early institution of avoidance measures, preventing progression to more serious disease.

7. Animal models

It is known that latex allergy is mediated through IgE mechanisms, however, the immunopathogenesis of the disease is not completely understood [97]. Furthermore, many questions remain including the relative importance of individual proteins, the role of the route of exposure, and the potential for concurrent exposure to other chemicals/contaminants in the environment to modulate the immune response to latex proteins. Animal models of latex allergy have been developed in order to begin to investigate these questions.

Numerous aspects of the immunopathogenesis of latex allergy have been demonstrated to be similar between animals and man. Aamir et al. [98], demonstrated that the cutaneous response to latex proteins in guinea pigs was mediated by IgE, and they were able to induce systemic anaphylaxis to latex proteins in these animals using a passive systemic anaphylaxis assay (PSA). Similar responses have been demonstrated in rabbits [99]. Following exposure to latex proteins, mice demonstrated elevated levels of total and latex specific IgE [100–103] and elevations in peripheral blood eosinophils [100,103]. Exposure to latex proteins has been shown to induce increased airway hyperreactivity in mice following non-specific and antigen-specific challenge [101–103].

Guinea pigs have been used to evaluate the immunogenicity and allergenicity of latex proteins [98]. Of the fractions (ranging from <10 to >106 kDa) of proteins from NAL extract tested, with the exception of the fraction containing proteins in the molecular weight range of 17–21 kDa, all induced dermal responses when tested by passive cutaneous anaphylaxis (PCA). These findings are consistent with later human studies in which skin testing with recombinant individual proteins (Hev b 2, 3, 5, 6, 7, and 8) demonstrated positive SPT in patients sensitized to multiple proteins [24]. Using the PSA, anaphylaxis and death were observed in guinea pigs passively receiving sera from animals immunized with NAL or the 24- or $\sim$45-kDa fractions, which were detergent-extracted from rubber cream, and subsequently intravenously injected with NAL.

Little is known concerning the role of the route of exposure in the development of latex sensitization. Animal models have demonstrated the potential for the development of sensitization following subcutaneous (SC), intratracheal (IT), intranasal (IN), and topical exposure to latex proteins. BALB/c mice were shown to exhibit time course and dose-dependant increases in total IgE following exposure by each of these routes [102]. SC exposure, to as little as 12.5 μg once a week for 2 weeks, was shown to induce a significant elevation in IgE. Topical exposure 5 days a week to abraded skin resulted in elevations in IgE within 23 days when 50 μg of latex protein was applied, and in as few as 16 days when exposure was to 150 μg. In vitro penetration studies using hairless guinea pig skin and human surgical specimens demonstrated that the amount of protein penetrating into and through the skin was positively correlated to the degree of dermal abrasion [14]. Although exposure to intact skin resulted in a delay in the elevation of IgE, by day 53 post-initial exposure, no significant differences were observed in IgE levels between mice exposed through intact or abraded skin. Exposure via the respiratory tract led to increases in total IgE in as few as 21 and 41 days by the IT and IN routes, respectively [102].

Exposure to latex proteins via multiple routes has been shown to be associated with pulmonary effects. Sensitization via respiratory tract [101–103] or dermal [102] exposure has been shown to induce increased airway hyperreactivity. Alterations in pulmonary histopathology have been demonstrated in animals sensitized to NRL by SC and respiratory routes [99,100].

Immunoblot analysis of the sera from animals exposed to latex via various routes supports the hypothesis that the route of exposure is responsible in part for the different profiles of sero-recognition observed in latex-allergic populations, i.e. health care workers versus SB patients. Mice exposed SC demonstrated increased recognition of proteins with approximate molecular weights of 14 and 27 kDa, while animals exposed via the topical or respiratory routes demonstrated a higher degree of sero-recognition of proteins with molecular weights near 14, 35 and 92 kDa [102].

Murine models are being used to investigate the potential for concurrent exposure to endotoxin and chemicals in the environment to modulate the immune response to latex proteins. Based on demonstrating high levels of endotoxin of respirable size associated with powdered latex examination gloves, Williams and Halsey [20] hypothesized that responses to endotoxin may be in part responsible for the clinical signs associated with latex allergy and that endotoxin may augment the IgE response to latex proteins. Investigations, using animal models, into the effects of concurrent exposure to endotoxin and latex proteins have revealed differing responses. Slater et al. [104], demonstrated an augmentation of the IgE, IgG1, and IgG2a response to a fusion protein containing Hev b 5 when endotoxin was co-administered by the IN route. Studies in NIOSH laboratories (data presented in abstract form only) demonstrated a decrease in total and latex specific IgE and a dose-responsive increase in IgG2a following IN co-administration of endotoxin and NAL proteins. The differences observed between these studies may result from exposure to a single protein in the studies performed by Slater et al. as compared to a complex mixture containing numerous different proteins in the latter studies. As shown in Table 1, numerous chemicals are used in the manufacture of latex gloves, many of which remain on the product as contaminants and are known to be irritants or to induce sensitization. Little is known of the potential for these chemicals to modulate the IgE response to latex proteins.

8. Conclusions

In the past decade, much information on latex allergy has been generated. We have gained an understanding of the clinical history, gained experience in recognizing symptoms, and identified major risk factors and groups. By studying the allergens, routes of exposure, and exploring animal models, information necessary to prevent most potentially life-threatening reactions has been obtained. Substitution of powdered latex gloves with low-protein powder-free or synthetic alternatives appears to be reducing the frequency of latex allergy in health care workers. However, considerable work still lies ahead. Information about the natural history of latex allergy and progression of the disease is still lacking. The diagnosis of latex allergy continues to be problematic in the US because no licensed skin test reagent is available and the approved serological tests have less than optimal performance characteristics. The development of standardized or recombinant latex reagents holds promise for increased testing accuracy and the potential for immunotherapy. Continuing education can help latex-allergic patients avoid products causing reactions and provide a reasoned approach to managing their disease.

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