

# Latex hypersensitivity in children

Ralph J. Cahaly, MD\*, and Jay E. Slater, MD\*†

\*Children's National Medical Center and †George Washington University Medical Center, Washington, DC, USA

Latex is a natural substance used in the manufacture of thousands of products. Although latex allergy is uncommon in the general population, health care workers and children with spina bifida appear to be at high risk for latex allergy. These patients may experience urticaria, rhinoconjunctivitis, bronchospasm, and anaphylaxis following contact with or inhalation of latex antigens. Several protein allergens in latex have been identified, some of which appear to cross-react clinically and immunochemically with fruit antigens. Good diagnostic tests are available for latex allergy, but strict avoidance is still the only available treatment.

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Since its initial description in 1979 [1], latex allergy has been a medical problem of increasing significance. More than 1000 anaphylactic reactions to latex medical devices had been reported to the US Food and Drug Administration as of April 1992, including 15 deaths [2•]. Of particular concern has been the ubiquity of latex devices, especially in the health care setting; it is used in the production of more than 40,000 medical and household products [3].

Latex is a milky white substance isolated from the sap of the commercial rubber tree, *Hevea brasiliensis*. A highly specialized cytosol, latex contains a remarkable number of allergens; Alenius *et al.* [4] identified 240 distinct polypeptides in latex, of which 57 bound IgE from latex-allergic patients. Although *Hevea* latex goes through extensive processing, some latex devices may contain as much as 2% protein by weight, and numerous studies have shown that antigenic protein is still found in significant concentrations in many latex products.

In this article, we focus on IgE-mediated (type I) reactions to latex, which are elicited by such protein antigens. We do not address the more common but less severe problem of contact dermatitis to latex, which is caused by a type IV hypersensitivity to chemicals added to these products during manufacturing [5].

## Risk groups for latex allergy

The risk of latex allergy in the general population appears to be low, perhaps between 0.1% and 1%. In con-

trast, two groups of patients have been described with significantly greater risk. Among children with spina bifida, the prevalence of significant titers of latex-specific IgE ranges from 28% to 67%. Among health care workers, the prevalence ranges from 2.6% to 16.9%. As with other allergic diseases, only a fraction — perhaps 25% to 50% — of patients with latex-specific IgE are clinically hypersensitive to latex [6•].

Kwittken *et al.* [7•] examined 35 patients with latex allergy who presented at Children's Hospital of Philadelphia over a 2-year period. Of these patients, 15 had spina bifida and a ventriculoperitoneal shunt, two had spina bifida alone, six had a ventriculoperitoneal shunt alone, four had exstrophy of the bladder, and one had spina bifida, a ventriculoperitoneal shunt, and bladder exstrophy. Spina bifida and bladder exstrophy cases represented 60% of the cases of latex allergy. The mean age of patients was 9.6 years, and 63% were male. Multiple surgical procedures at an early age were common; each of the 17 spina bifida patients underwent surgery in the first 2 weeks of life, and 17 of the 18 other latex allergic patients underwent surgery by 1 year of age. Notably, only 18 (51%) of the patients had a prior history of hypersensitivity reactions to latex. In 14 of the 35 patients, reactions were attributed to injection of medication through a latex intravenous injection site.

In another study at Children's Hospital of Philadelphia, Dormans *et al.* [8] investigated 21 consecutive patients who had experienced intraoperative anaphylaxis attributed to latex. Of these, 57% had spina bifida and 29% had cerebral palsy; 76% of these patients had ventriculoperitoneal shunts. These patients had experienced an average of 11 surgical procedures prior to

## Abbreviation

RAST—radioallergosorbent test.

their anaphylactic reactions. In another study by Kelly *et al.* [9•], 10 of 11 patients with intraoperative anaphylaxis due to latex had spina bifida; 1 of 11 had a congenital urologic abnormality. These patients were compared with age- and gender-matched spina bifida patients who underwent uneventful surgery. The anaphylactic patients were more likely to have a history of asthma, food allergy, or multiple surgical procedures. They were also more likely to have had daily rectal disimpaction.

Is the remarkably high prevalence of latex allergy among spina bifida and bladder exstrophy patients due to frequent exposure to latex at an early age or to other factors? Konz *et al.* [10•] compared the prevalence of latex-specific IgE in 36 children with spina bifida, 50 patients with spinal cord injury, and 10 patients with cerebrovascular events. Whereas spina bifida patients and spinal cord injury patients had similar frequencies of latex exposure (from surgery, rectal disimpaction, and bladder catheterization), only 4% of spinal cord injury patients, compared with 72% of spina bifida patients, had elevated titers of latex-specific IgE. The authors noted that the exposure in spina bifida patients occurred much earlier in life than in the spinal cord injury patients. Pittman *et al.* [11••] compared children with spina bifida with children with a history of at least three surgical procedures. Among the spina bifida group, 39 of 83 (47%) had latex-specific IgE, whereas only six of 40 (16%) of the multiple surgery group had a positive latex radioallergosorbent test (RAST). Interestingly, in both groups the likelihood of a positive latex skin test result increased with the number of surgical procedures.

Among adults, health care workers appear to be at significantly greater risk of latex allergy than the general population. Charous *et al.* [2••] studied 47 health care workers with occupational latex allergy. Among those with systemic reactions, 15 of 24 (62%) had a history of contact dermatitis to gloves preceding the development of systemic symptoms. Other risk factors included atopy, food allergy, and drug allergy. Notably, in this group, the IgE-mediated reactions took longer to develop than the cell-mediated reactions. More than half of contact dermatitis subjects developed symptoms within 20 months of occupational latex exposure, whereas it took an average of 40 months for patients with chronic urticaria and 100 months for patients with systemic reactions to develop symptoms.

### Latex allergens in medical gloves

Although latex antigens may be found in numerous medical and nonmedical devices, latex gloves are probably the major source of exposure for spina bifida patients and health care workers alike. Yunginger *et al.* [12••] examined 71 lots of rubber gloves using pooled sera from five latex-allergic health care workers. The

authors found that powdered gloves had higher levels of latex antigen than powder-free gloves and that allergen levels varied 3000-fold among different manufacturers. They also found that allergen levels were higher in examination gloves than in surgical or chemotherapy gloves. Allergen levels in toy balloons were found to be comparable to levels found in powdered gloves. Low levels of antigen were found in condoms, baby bottle nipples, pacifiers, and intravenous connectors and tubing. In another report, Jones *et al.* [13] noted little overall reduction in antigen content among most glove brands studied over a 3-year period. Alenius *et al.* [14] found that extracts from five of seven different brands of latex gloves produced positive skin test results in latex-allergic patients. Beezhold *et al.* [5] found that unpowdered gloves transferred less latex allergen to the user than powdered gloves. Washing the powdered gloves did not significantly lower the amount of antigen transferred, and using hand cream prior to donning gloves actually raised the amount of antigen transferred.

### Occupational asthma due to latex in hospitals

Pisati *et al.* [15] studied four nurses who developed bronchospasms when working with powdered latex gloves. On challenge, all four nurses developed bronchospasm from handling powdered gloves as well as from nebulized powdered glove extracts. Nebulized cornstarch resulted in no bronchospasm, and powder-free glove extracts resulted in less severe bronchospasm. Valentino *et al.* [16] also reported on four hospital personnel who experienced wheezing when coworkers used latex gloves.

These and similar observations have suggested that the cornstarch used to lubricate most latex gloves may adsorb latex proteins and carry them into the air. Tomazic *et al.* [17•] showed that cornstarch extracted from latex gloves completely inhibited a latex RAST assay. Unexposed ("virgin") cornstarch did not inhibit the assay, suggesting that cornstarch that has coated latex films can serve as an aerosol vector for antigen. Swanson *et al.* [18••] quantified levels of latex antigen in various areas of the Mayo Medical Center and found that areas where powdered latex gloves were used had elevated levels of latex antigens in the air, 20% of which were on respirable particles. Large quantities of antigens were also isolated from scrub suits, laboratory coats, and laboratory surfaces. In contrast, in the bone marrow transplant unit, where only nonpowdered latex gloves were used, latex aeroallergen levels were nondetectable.

### Asthma due to latex outside the hospital

Airborne latex antigens have also been found outside the hospital. Orfan *et al.* [19] described two sub-

jects who developed occupational asthma working in a doll manufacturing plant where sanding of latex doll parts was done; both had positive skin tests to latex. Williams *et al.* [20•] sampled the air in two outdoor locations in Denver and found numerous irregular black particles. These particles were identical to those found in milled rubber tire samples and, using latex RAST inhibition studies, appeared to contain latex protein antigens.

## Fruit and latex antigen cross-reactivity

As with other allergens, latex proteins cross-react with proteins from apparently unrelated species. Blanco *et al.* [21•] studied 25 patients with latex allergy and found 42 food allergies in 13 of the 25 patients (52%). The most frequent food allergies found were avocado (nine cases), chestnut (nine cases), banana (seven cases), kiwi (five cases), and papaya (three cases). RAST inhibition studies showed cross-reactivity between latex, avocado, chestnut, and banana. In five cases latex allergy came before the food allergy, in five cases the onset was simultaneous, and in three cases the food allergy came first. Makinen-Kiljunen [22] examined 47 patients with a history of latex allergy. They found that 66% had a positive latex RAST and that 55% had a positive banana RAST. Both latex and banana were cross-reactive by RAST inhibition with pooled sera. Of the 31 sera with positive latex RAST, 81% had positive banana RAST, whereas only 1 of 16 latex RAST-negative sera had a positive banana RAST.

Adverse reactions to inadvertent oral ingestion of latex have been reported as well. Schwartz [23] reported on one patient who developed urticaria and another who developed urticaria, angioedema, and dyspnea in a fast food restaurant where latex gloves were used in the preparation of food. Both patients had positive skin tests to latex.

## Identification of specific latex antigens

The identification and characterization of latex antigens will have implications for the prevention and treatment of latex allergy. Unfortunately, different methods have, at times, yielded conflicting results. The most frequently reported technique is immunoblotting, or Western blot. Alenius *et al.* [24] found at least 30 proteins in rubber tree sap, of which 19 bound IgE from latex-allergic subjects. The 14-, 30-, 36-, 39-, 44-, 46-, 54-, and 75-kD proteins were bound most frequently by sera from the 27 subjects in this study. The authors noted that 10-, 14-, 20-, 30-, and 100-kD proteins have been reported in two or more studies as binding latex-allergic sera. Lavaud *et al.* [25•] examined serum samples from 17 patients with well-documented latex

allergy, 10 of which showed allergy to avocado and sometimes banana. All of the sera from patients allergic to latex and fruit bound a 30-kD band present in both crude latex and extracts of avocado and banana. Only one serum from the group allergic to latex but not fruit bound this same 30-kD band. Yagami *et al.* [26] isolated a protein from latex and glove extracts that had lysozymal activity. The protein was found to be 27 kD in size and bound to IgE from serum of a latex-allergic housewife. Similar proteins with lysozymal activity have been described in avocado, papaya, and fig, and the authors concluded that this 27-kD protein may be the latex antigen responsible for cross-reactivity with certain fruits. Slater and Trybul [27] produced a monoclonal antibody that recognizes a 14-kD band of latex allergens. This 14-kD antigen was found to bind sera from 14 of 14 spina bifida patients with severe latex reactions who were studied. Interestingly, this monoclonal antibody bound specifically to other bands as well, raising the possibility that identical epitopes appear on distinct peptides in these analyses. A possible explanation for this finding is that a parent peptide, bearing the epitope, is cleaved into multiple products, each of which may contain the epitope in question.

## Diagnosis and treatment

The diagnosis of latex allergy is made by obtaining a careful history and by judicious use of diagnostic tests as appropriate. At present, no standard commercial latex extract is available in the United States, so the RAST has become the mainstay of testing in this country. Patients who have no history of adverse reactions to latex products and are not in a high-risk group (spina bifida, genitourinary abnormalities, health care workers) need no special testing. Patients with a history of adverse reactions to latex, especially those in a high-risk group, should have a serum RAST or enzyme-linked immunosorbent assay to look for latex-specific IgE. The sensitivity of these tests can vary depending on the laboratory performing the test and the extract used. For instance, extracts made from different brands of latex gloves may have different antigens present than extracts made from crude latex. Most latex is ammoniated prior to manufacture, so many investigators use extracts of ammoniated latex for testing.

Hamilton *et al.* [28•] attempted to detect latex-specific IgE in 56 latex-allergic patients using ammoniated latex extracts, nonammoniated latex extracts, and glove extracts. They found that all types of extracts had similar sensitivities, but the tests still only detected two thirds of patients with a history of a systemic reaction to latex. Murali *et al.* [3] investigated the human cellular responses to latex allergens. They studied 16 patients with positive skin tests to latex and found that their lymphocytes proliferated in response to incubation with latex antigen significantly more than those from control subjects. The authors were also able

to demonstrate *in vitro* IgE synthesis to latex by patients' lymphocytes. These effects were especially pronounced in patients with spina bifida.

## Conclusions

Latex allergy has become a significant medical problem, especially for health care workers and patients with spina bifida. There is good evidence of cross-reactivity with several fruits. Gloves are a major source of antigen, and cornstarch is an important vector for the aerosolization of latex peptides. With careful history-taking and appropriate use of diagnostic tests, most patients with latex allergy can be identified readily. Strict latex allergen avoidance remains the only effective method of treatment [29•].

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Ralph J. Cahaly, MD, and Jay E. Slater, MD, Children's National Medical Center, 111 Michigan Ave, NW, Washington, DC 20010, USA.