

# Latex Allergy: Where Are We Now and How Did We Get There?



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**Latex allergy emerged as an epidemic of anaphylaxis, occupational asthma, and clinical dilemmas in the 1980s. A systematic recognition, investigation, discovery, epidemiology, and prevention strategy followed. International attention and collaborations of investigators, government agencies, manufacturing, and health policy resulted in near elimination of a global epidemic. This article summarizes nearly 4 decades of work in control of this epidemic and focuses attention on future problems that still require resolution. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1212-6)**

**Key words:** Natural rubber latex; *Hevea brasiliensis*; Anaphylaxis; Occupational asthma; Latex gloves; Skin testing; Serologic testing; *Spina bifida*; Health care workers

Nearly 4 decades have passed since the first modern case of IgE-mediated natural rubber latex (NRL) allergy was reported.<sup>1</sup> Subsequently, a worldwide epidemic of allergy and anaphylactic reactions to NRL proteins emerged, was systematically investigated, and nearly eliminated. Persistent sensitization is observed, and occasional new sensitization occurs as well.

Epidemics are frequently first recognized by astute clinicians who recognize a new constellation of signs and symptoms in patients that are not explained by known exposures or vectors. Latex allergy resolution represents a notable collaboration of medical clinicians, researchers, manufacturers, the Centers for Disease Control and Prevention, the National Institute of Occupational Safety and Health (NIOSH), and the Food and Drug Administration to control an epidemic. This global collaboration of multiple research groups proceeded with synergy

between the United Kingdom, Europe, Scandinavia, Canada, the United States, Southeast Asia, Japan, Australia, and South America. At its peak, up to 17% of health care workers (HCWs) had become sensitized to latex, compromising their ability to work in the health care industry,<sup>2</sup> as had 70% of all patients with spina bifida<sup>3</sup> who were at risk of death during surgical operations and daily care of their medical conditions. Today, we see less than 1% of the population developing latex allergy.<sup>4-6</sup>

## THE EPIDEMIC

During the 1980s to 1990s, the risk of sensitization to NRL became very high for HCWs, patients with spina bifida, genital-urinary tract anomalies, and neurologic defects, patients requiring multiple surgeries, atopic individuals, and workers in industries that manufactured rubber products.<sup>7-18</sup>

In 1927, a single case of chronic urticaria from rubber prosthetics was reported in Germany.<sup>19</sup> Fifty years passed until a second case of latex allergy was confirmed by dermatitis, urticaria, and pruritus in a homemaker to rubber gloves.<sup>1</sup> In the 1980s, latex allergy-induced rhinitis, asthma, and ocular symptoms in HCWs were identified by various authors in Europe. The growing prevalence of sensitization to latex in 2.9% of HCWs was confirmed in Finland. Indeed, operating room personnel were found to have the highest prevalence at 6.2% with a very strong association with atopic predisposition.<sup>20</sup>

In the same year, 5 individuals were reported with systemic reactions to latex gloves, but only 1 was an HCW.<sup>21</sup> It was not until 1989 that the first cases of occupational asthma to latex were reported.<sup>22</sup> Until that time, mucosal reactions of conjunctival irritation and rhinitis were believed to have come from direct allergen transfer. These sentinel case reports started to confirm an understanding that the environment was being contaminated by allergen-carrying glove powder.

In 1989, 2 children with spina bifida suffered anaphylactic reactions during surgery. Following an evaluation that excluded other causes and confirmed the presence of latex-specific IgE, these reactions were attributed to intraoperative latex exposure.<sup>23</sup> It was not until 1991 that investigators in the United States working with the Centers for Disease Control and Prevention identified a marked increase in anaphylactic reactions during surgical procedures.<sup>24</sup> This identification took place in Canada as well as the United States with distinctly different clinical scenarios.<sup>25</sup> In one case series, all the children had developed allergic reactions during the induction of anesthesia, whereas in the other case series mucosal contact with rubber gloves occurred intraoperatively.<sup>3</sup> The episodes of anaphylaxis in the operating room reached a heightened level in 1991 in the United States when in one hospital 1 out of every 8 patients with spina bifida developed anaphylaxis during induction of anesthesia, representing a 500-fold higher rate of anaphylaxis than expected from general

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anesthesia. The study identified that 100% of these patients had latex allergy.

A subsequent follow-up study of the prevalence of latex allergy found that nearly 70% of all patients with spina bifida in one center were skin test positive to latex allergens; skin prick testing with a glove extract caused not only local reactions, but some systemic reactions as well.<sup>7</sup> The risk factors identified during this period of time for sensitization to latex included atopy, multiple surgeries, rectal mucosal contact from latex gloves for bowel disimpaction, and skin test reactivity to some fresh fruits.

### **Other patients with urologic, neurologic defects, or multiple surgeries**

In addition to patients with spina bifida, individuals who had other multiple surgeries,<sup>8</sup> especially those with cloacal anomalies, were experiencing anaphylactic reactions in the operating room. In addition, children with other congenital anomalies such as esophageal atresia, gastroschisis, omphalocele, and neurologic disease such as cerebral palsy may have a higher prevalence of latex allergy.<sup>8</sup> Patients with spinal cord injuries became the natural control group to study to see whether they were also at risk for developing latex allergies. Conflicting results, probably because of small study size, demonstrated that other neurologic injuries, such as spinal cord injury, were not a significant risk for the development of latex allergy.<sup>12</sup> However, a second study found approximately 15% sensitization rate, but a 4% clinical reaction rate.<sup>13</sup>

### **Health care workers**

Clinical manifestations of latex allergy in HCWs were unique. Most were found to have an irritant or contact hand dermatitis when they wore gloves, with this predicting symptoms of latex allergy 11 times more frequently than those who did not have dermatitis.<sup>26</sup> In 1 hospital 17% of HCWs were found to be sensitized to latex and 50% of these individuals appeared to have respiratory asthma like symptoms from exposure to gloves in their work environment.<sup>2</sup> In fact, many individuals were having clinical reactions on entering the operating room or other medical parts of the facility without specifically donning latex gloves for personal use.

### **Patients with type 1 diabetes mellitus**

Another group of patients described with latex allergy were type 1 diabetics using rubber-topped insulin bottles. These were punctured repetitively and some patients developed latex allergy. These observations resulted in concerns about medications delivered to latex-allergic individuals.<sup>27-31</sup>

### **General populations**

To confirm that the risk groups were limited to the subsets of the patients, prevalence studies were undertaken in the general population. Approximately 1% (range, 0.7%-1.1%) were found to have sensitization to latex.<sup>4,5</sup> Interestingly, in the early 1980s, another epidemic of anaphylaxis occurred with up to 148 episodes of anaphylaxis and 9 deaths associated with rectal mucosal exposure to an air contrast barium enema catheters that had a latex-tipped balloon.<sup>32</sup> Only in retrospect does it appear that these were patients sensitized to latex who were exposed to rectal balloons through manometry or barium retention enemas.<sup>33</sup> It appears that many of those subjects were not HCWs

and did not have specific risk factors. There is a risk, albeit not a high prevalence risk, in the general population for the development of latex allergy in some individuals.

### **Why did the epidemic occur and how was it controlled?**

The emergence of the latex allergy epidemic resulted from a confluence of several changes in health care delivery. The emergence of human-to-human transmission of infectious pathogens such as hepatitis C and HIV resulted, in 1987, in the promotion of Universal Precautions to protect workers from acquisition of disease. These precautions have now become known as "Standard Precautions" but resulted in a massive increase in the use of latex examination gloves in health care and other industries (eg, food handling). Before the implementation of these precautions, approximately 300 million units of examination gloves were sold in the United States but by the end of the 1990s, this had risen to approximately 36 billion units of examination gloves for a more than 100-fold rise in volume.<sup>34</sup>

In addition, a change to the use of cornstarch donning powder from talc inadvertently may have created an extremely efficient carrier of latex allergens to skin and airborne environments.

Additional speculation suggested that before the implementation of standard precautions, NRL harvested at rubber tree plantations was stored for up to 6 months before being used in the manufacturing process. That prolonged storage may have resulted in degradation of protein allergens. With purchasing pressure for latex gloves in the health care industry, that storage time may have declined to as little as 2 weeks, resulting in a possible higher content of allergen entering the finished latex product.<sup>34</sup>

Regardless of the other contributing causes, increased exposure to NRL glove allergens was the common factor that paralleled the rise in the prevalence of the disease. Sentinel occupational work in Germany by Allmers et al,<sup>35</sup> latex avoidance from birth for patients with spina bifida,<sup>36</sup> and 2 critical incidence studies from Canada<sup>15</sup> and the United States<sup>37</sup> resulted in the identification of powdered latex examination gloves as the causative agent for the epidemic. A change to nonpowdered latex and synthetic examination gloves dramatically reduced sensitization. More importantly, the US study from Wisconsin demonstrated that 25% of sensitized HCWs lost evidence of skin test reactivity after occupational avoidance of powdered latex gloves.

Simultaneously, latex precautions<sup>36</sup> promoted by the American Academy of Asthma, Allergy & Immunology, the American College of Asthma, Allergy & Immunology, and the Association of Operating Room Nurses in the United States resulted in safer care of patients with latex allergy. NIOSH also adopted these measures and produced an alert for use by health care professionals in 1998.<sup>38</sup> However, it was the scientific and epidemiology work across the globe that resulted in a final understanding that the latex allergen content of gloves and environmental contamination through the air of allergen carried by cornstarch powder was the cause of the epidemic. This finally resulted in the Food and Drug Administration banning the sale of powdered surgeon gloves, powdered patient examination gloves, and absorbable powder for lubrication of surgeons gloves in the United States in January 2017 that should keep this disease under control.

## Latex allergens and latex-fruit syndrome

NRL is an intracellular cytosol secreted into a lactiferous plant's circulation system. Latex carries defense proteins to prevent herbivores from attacking the plant. Although more than 12,000 plant species yield latex containing rubber derived from cis-1,4 polyisoprene, only a few plants produce rubber suitable for manufacturing. The universal source of NRL in manufacturing was from the rubber tree *Hevea brasiliensis* and is harvested almost exclusively in southeast Asia.<sup>34,37,39</sup>

Although NRL may contain more than 240 protein peptides, 15 allergens (*Hev b 1-15*) have been well characterized and designated by the World Health Organization/International Union of Immunologic Societies allergen nomenclature committee. Specific latex allergens can be associated with specific clinical patterns of reaction. Allergens *Hev b 1* and *Hev b 3* are membrane-bound elongation proteins that are uniquely associated with latex allergy in patients with spina bifida. These critical findings suggest that exposure to latex gloves may not be the sole reason for the development of latex allergy in this population. Other sources of latex, route of latex exposure, age when first exposure to latex occurs, and genetic factors of these individuals make this population's propensity to develop latex allergy unique and incompletely understood.

The remaining identified allergens appear to mostly belong to the families of defense proteins and common allergens found in fruits and vegetables such as lipid transfer proteins or profilin.

*Hev b 6* (hevein) makes up a substantial amount of the total protein in latex. It has significant cross-reactivity to chitinases in banana, avocado, and chestnut and gives rise to the "latex-fruit" syndrome where latex-allergic patients develop allergic symptoms after eating one of these fruits. More than 25 different fruits have been found to have some degree of cross-reactivity with latex.

*Hev b 5* is a significant allergen to HCWs and shows significant homology to a kiwi allergen. It is a critical component for reagents in serologic and skin testing for latex allergy, resulting in increased sensitivity.

*Hev b 7* has considerable homology with patatin, a storage protein in *Solanaceae* (eg, potato or eggplant), resulting in cross-reactivity with these plants.

*Hev b 8* is a profilin contained in numerous plants and does cross-react with many pollens that contain profilins. It is believed that some subjects who have a positive skin or serologic assay, but no evidence of clinical latex allergy, may be primarily sensitized to pollens. There is also cross-reactivity with kiwi and avocado and this allergen, which may explain some of the clinical symptoms seen with the ingestion of these foods. Sorting this complex situation out may require the use of allergen component testing *in vitro* to separate allergens.

The other well-characterized latex allergens appear to be minor contributors to the allergic sensitization to latex.

*Hev b 12* is a lipid transfer protein. Lipid transfer proteins are highly cross-reactive in multiple plant species.

It is important to understand that not all patients with latex allergy have clinical reactions to fruit. It has been estimated that 50% of latex-allergic patients have clinical symptoms to 1 (common) or more (uncommon) fruit. In contrast, only 10% of patients with known primary allergy to a fruit cross-reacting with latex develop latex symptoms.

## DIAGNOSIS OF LATEX ALLERGY

A diagnosis of latex allergy requires a complete medical history and physical examination that is then supplemented with appropriate testing. The use of skin testing and/or serologic testing as screening tests is not appropriate given the performance of these tests in the general population.

Studies of skin testing with multiple sources of latex proteins (eg, nonammoniated latex and a latex glove extract) yield a high sensitivity for a diagnosis of latex allergy. However, anaphylactic reactions following glove extract skin testing precluded the use in the United States.<sup>7,40</sup> The multicenter skin test study with a single source of latex protein (clone 600) at 2 concentrations showed the skin test to be 95% to 99% sensitive and 96% to 100% specific based on the medical history.<sup>41</sup> Adverse reactions, mostly minor, were as high as 10-fold greater than skin tests with pollen extracts in one center,<sup>40</sup> and occurred at a rate of 16.1% in the multicenter skin test study.

Serologic testing in this same population showed the Immunocap (Phadia, Uppsala) assay to have a sensitivity of only 76% and the AlaSTAT 73%.<sup>42</sup> In a later study of HCWs who underwent duplicate skin tests with nonammoniated latex from clone 600, the sensitivity of the Immunocap was only 35% but with high specificity.<sup>43</sup>

Although subsequent studies using novel technologies for measuring specific IgE, or combinations of recombinant allergens, have improved diagnostic performance, these approaches are not readily available, and skin test reagents remain unavailable in the United States.<sup>44</sup> Thus, clinicians remain without good, validated diagnostics for this important allergy. If the medical history and Immunocap assay are both positive, an appropriate diagnosis is highly likely. However, when a patient with a reasonable story consistent with latex allergy has a negative Immunocap test result, they still may be at a significant risk of a latex-induced reaction.

## WHERE DO WE GO FROM HERE?

Patients with spina bifida, individuals who repetitively use latex gloves, and atopic individuals appear to remain at a higher risk than the general population for the development of latex allergy.

Over the past 15 years, manufacturers of latex gloves adapted to this emergent crisis by making substantial changes to the manufacture of medical gloves. NRL gloves gradually became cornstarch powder free to eliminate environmental contamination with latex-laden powder, and the gloves themselves had reduced NRL allergen content most likely associated with a chlorination process. But one of the most significant changes was the development of a synthetic rubber glove made from nitrile butadiene rubber. The glove industry adapted to the changing landscape, which took many years of research in polymer chemistry to produce gloves with equivalent tear and puncture resistance, virus impermeability, elasticity, and modulus (the return to the original shape after stretching).

Health policy contributed to the reduction in the prevalence of this disease. In January 2017, a ban on the manufacture and sale of most powdered medical gloves in the United States was imposed.<sup>45</sup>

The problems not yet resolved are included in [Table I](#). Although the incidence and prevalence of latex allergy have

**TABLE I.** Unresolved issues in latex allergy

FDA-cleared latex skin test reagent
Improved sensitivity of latex-specific IgE serologic assays
Managing daily lives of patients with persistent latex allergy
How do patients with spina bifida get sensitized?
What is the source of sensitization to latex in the general population?
Can we get all occupational-induced latex-allergic patients back to work?
What happens to the occupational asthma of latex allergy over time?
Can we eliminate type 4 contact dermatitis to additive chemicals in all gloves through better manufacturing?
Educating health care providers about latex allergy with its lower prevalence
What should be done with multiple-dose vials that have NRL tops (eg, vaccine)?

FDA, Food and Drug Administration.

decreased, for those affected serious concerns and uncertainty remain.

Up-to-date practical guidelines for latex allergy precautions are needed. Most nonmedical rubber products have little allergen in them due to prolonged heating during manufacture, chemical solvent use, and other methods. Avoidance lists that fail to distinguish among products on the basis of allergen content and bioavailability only heighten the anxiety of inadvertent contact causing an allergic reaction.

Patients need to be mostly concerned about products made by a dipping method with low heat and minimal time vulcanization. These include NRL gloves, condoms, NRL catheters, household gloves, finger cots, some clothing, balloons, and medical devices that contact mucosal and vascular surfaces.

Patients with spina bifida should continue to avoid all latex from birth. There is no adequate explanation of their unique risks. Physicians, especially urologists, neurosurgeons, and orthopedic surgeons, need to remain vigilant in their crucial care for this population.

Skin testing is unlikely to advance further unless already approved reagents in Europe and Canada are allowed to be cleared through the Food and Drug Administration. In the United States and Canada, it is unlikely that serologic tests will improve without a skin test to compare the sensitivity, specificity, and predictive values.

Occupational latex-induced asthma and occupational latex allergy need to be consistently reviewed by the NIOSH and professional experts. It is unclear whether latex-induced asthma will remain active with the reduction in airborne latex exposure as seen in western red cedar workers.

In addition, the steady reduction in HCW latex allergy may be due in part to the phenomenon of the "healthy survivor" found in one study.<sup>37</sup> The natural attrition of employment was nearly triple in latex-allergic HCWs. They left the institution on their own accord without follow-up and possibly to protect their personal health.

Hand dermatitis remains a significant risk in HCWs who develop latex allergy. Individuals who became sensitized to rubber additives including mercaptobenzothiazole, thiuram, or carbamate could have problems with nitrile and vinyl gloves that contain these chemicals. Manufacturing must strive to create highly functional medical gloves without residual chemicals.

Multiple-dose vials including parenteral medications and vaccines with NRL as the access point for needles/syringes should not be punctured repeatedly. This restriction is not presently in place and may result in some adverse events in some who get sensitized or are already latex allergic from this contact. Fortunately, most multiple-dose vials no longer use NRL as the stopper.

## SUMMARY

Latex allergy rapidly emerged for the field of allergy/immunology to recognize, report, research, make recommendations, testify to Congress, work with government agencies and industry, and eliminate this epidemic. The lifetime loss of a nurse or physician from health care results in multiple millions of dollars of lost productivity and training replacement. With 50% of latex-sensitized HCWs developing asthma, they would need to be removed from patient care areas if powdered latex examination gloves are still used. At the peak of latex allergy in HCWs, there were approximately 825,000 US physicians and 2,725,000 nurses. With a prevalence of 10% sensitization and a removal from work of 50% of those sensitized workers due to asthma, there would have been a replacement cost to the medical industry that could have exceeded \$300 billion.

The recognition and management of the latex allergy epidemic was a massive collaboration resulting in lives saved, jobs saved, and prevention of an economic disaster. Additional research is required and hopefully will be funded to reach the finish line of this journey.

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