Latex Allergy Overview

I. Common latex allergy signs
   a. Hives.
   b. Hay fever-like symptoms
   c. Anaphylaxis (vascular collapse – can't breathe) is most dangerous

II. Some latex reactions are not really latex allergies
   a. Irritant dermatitis from taking things on and off often causes irritation
      1. Not caused by latex
      2. Caused by irritation of the skin
   b. Contact dermatitis from other types of products that are mistakenly labeled as latex

III. True latex allergy is really an IgE mediated allergic reaction
   a. Body is exposed to antigen proteins in the latex
   b. Body makes IgE antibodies
   c. IgE bonds inside body and process continues until reaction develops

IV. Latex allergies have been reported since 1930s
   a. Initial reports from Germany
   b. Reports almost all from use of rubber gloves, condoms, catheters, adhesives
   c. More reports now because of increased use of rubber gloves in the past 15 years; not necessarily more people developing latex allergies
   d. Reactions in general population not common
   e. Most reports from health-care field

V. Latex is a natural product
   a. Any natural product will have potential for allergic reaction
   b. The protein is called pure cis-1-4-polyisprene that is found in latex in the rubber

VI. Latex was discovered and made to be stable at temperature
   a. Firestone discovered that by adding sulfur in the presence of heat (vulcanization) that latex can be made stable (rubber)
   b. Early attempts at making things from latex from trees involved dipping garments in the latex, but latex flaked off when it got warm

VII. Dipped latex products (instead of molded products) seem to be the types that cause reactions
   a. Gloves and condoms are dipped products – almost all reactions come from products like this
   b. Molded products (tires or mattresses) are not know for causing reactions
      1. Molded products made at higher heat
      2. Dipped products made at lower heat
      3. Higher heat seems to inhibit the proteins (IgE) that cause latex allergies

VIII. Powder used in latex gloves seems to be a large problem in allergy mechanism
   a. Powder must be used as a lubricant in the gloves
   b. Powder is a efficient transmitter of the latex protein that causes the reaction
      1. Powder absorbs the latex antigen proteins
      2. Powder transmits these latex proteins efficiently on the surface of the powder to the skin
      3. Abrasion of the skin from frequently putting gloves on and off makes it easy for latex antigen proteins to enter the body
      4. Latex allergic reaction then has potential to develop

IX. Only two allergens commonly found in latex seem to cause reactions in any great numbers
   a. Hev b 1 allergen is all around us every day and is found in mattresses, pillows, seat cushions and gloves
      1. People are exposed to Hev b 1 in great amounts everywhere they go
      2. People breathe in large amounts of Hev b 1 every day in all locations
      3. If you don't get an allergic reaction the minute you walk into a location with latex, you will not get a reaction to this Hev b 1 (i.e., a mattress store)
   b. Hev b 5 is found in latex gloves and seems to be more reactive

X. Certain fruits or diseases increase the latex sensitivity of people

a. People in fruit industry who wear rubber gloves can have increased reaction to certain latex allergens
b. Certain diseases can cause the same type of increased sensitivities

Synopsis

While latex allergies do exist, they are not increasing in rate. They are simply being reported more often as more people use latex gloves. There are different types of latex allergies, but almost all reports of latex allergies come from people in the health care industry. Many of these reports of latex allergies are really different types of contact dermatitis from frequently taking any type of glove on and off during the course of a day.

The type of latex allergen found in latex mattresses is exposed to people in large amounts on a daily basis. These allergens are common and aren't a cause for concern in the mattress industry. A person would have an immediate reaction when walking into a mattress store if they were allergic to these types of allergens. The process of molding latex, like making a latex core for a mattress or making a car tire (vulcanization), does not seem to promote latex allergies; it instead seems to prohibit them. There is something about the heating process that seems to eliminate these allergens or to cause them to not be present in amounts to cause allergic reactions. You don't see people working in tires shops breaking out in hives, nor do you see the same thing in a mattress factory or store.

Conversely, dipped latex products, like gloves, do tend to produce reactions in a small amount of the population. The reasons for this are not entirely clear, but the lower temperature of the dipping process and the ease of antigen protein transmission from the powder used in latex gloves seem to be the major causes.

Basically, people don't tend to have reactions to the style of latex used in latex mattresses. Besides not containing the type of allergens normally associated with most latex allergies, these products are washed many times in the manufacturing process to reduce the presence of these antigen proteins / allergens. Additionally, the heat used in the molding process seems to reduce the presence of these products also.

Latex glove allergies are not the same as a latex mattress allergy (of which there is little evidence) and if someone does not have a reaction when walking into a mattress store, there is little evidence to show that they will have a reaction when sleeping on a latex mattress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

UNITED STATES FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

ADDITIVES AND INGREDIENTS SUBCOMMITTEE
OF THE
FOOD ADVISORY COMMITTEE

LATEX ALLERGY

Tuesday, August 26, 2003

9:10 a.m.

St. Regis Hotel
923 16th Street, Northwest
Crystal Ballroom
Washington, D.C.

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Basic Latex Allergy Background

DR. SLATER

Latex allergy is a clinical syndrome that is characterized by these kinds of clinical reactions upon exposure to natural rubber latex, and the reactions can be any or all of these types of reactions. It can be urticaria, which is hives, rhinoconjunctivitis, the sort of standard hay fever symptoms, wheezing, and notice I use wheezing and not asthma, asthma being a chronic disease. This is acute wheezing associated with latex exposure.

Finally, the entity that we all fear the most is anaphylaxis, and anaphylaxis is a systemic multisystem allergic reaction that may include any or all of the above plus hypotension and general vascular collapse.

Now, there are other clinical syndromes that are called latex allergy, as well, and I am going to mention those to exclude them at this point. Contact urticaria, simple hiving at the spot where you are exposed to a substance can be the same kind of reaction as latex allergy, but there are certainly several case reports that suggest that some patients with contact urticaria alone have a different pathophysiologic mechanism going on.

Certainly, individuals with contact dermatitis, which is a poison ivy-like reaction on exposure to latex product, that is clearly a different pathophysiologic mechanism. This, by

the way, is a fairly common entity among healthcare workers and individuals who wear rubber gloves. It can also happen as a cause of foot dermatitis from rubber products that leach through the socks to the feet.

In addition, there is an entity that, for lack of a better term, is called irritant dermatitis, that happens in certain individuals especially when they take gloves and put them on and off, and the way we can distinguish this from latex-associated dermatitis is that this happens regardless of the construct of the glove that they are using. So, in other words, it would occur with non-latex gloves, as well.

What we are talking about here today are IgE mediated allergic reactions. This is sort of the standard garden variety allergy that you are probably all familiar with either from yourselves or from relatives who have hay fever. In IgE mediated allergy, antigen exposure leads to the generation of a specific antibody called IgE that recognizes that antigen. The IgE is manufactured, as are all antibodies, by plasma cells. It is released into the blood, diffuses into the interstitial tissue where it encounters mast cells and binds to the surface of those mast cells.

The mast cells then are primed and ready for the next exposure to allergen, that, in addition to eliciting further responses among the antigen-presenting cells, T cells and B cells, elicits a very rapid reaction in the tissue mast cells that leads to the release of mediators.

These mast cells are packed with granules, which you can see here, you can see granules being released. This release occurs not in minutes to hours, but literally in seconds, and you can talk to any individual who has been subjected to a ragweed inhalation challenge, and they know that they have inhaled ragweed instantaneously, it is very, very quick.

The mediators that are released immediately are histamine and certain proteins that are released, as well. Subsequently, other mediators that are not preformed are released. That can elicit just as significant types of reactions.

Latex allergy has actually been around for a while. The initial reports were in the German literature in the 1930s. These involved dental patients who reacted to exposure to latex during procedures. But then there was a hiatus of something on the order of 40 or 50 years before the next report appeared in 1979 in Europe, and that was followed by a series of reports in the European literature that really didn't receive much attention here on this side of the Atlantic, but retrospectively, really presaged our experience almost entirely.

The initial reports in North America were in 1989, and those reports were followed by a spate of reports throughout the world. The reports were all clinical reports in which the device that elicited the allergic reaction was listed, and most of these reports centered on latex gloves, but there certainly are plenty of reports in literature of reactions to other latex devices - condoms, catheters, cofferdams, which are basically large, open sheets of latex that are placed in the mouth or in other cavities to try to block the flow of fluid to a surgical site, surgical drains, what we used to call Penrose drains, have elicited reactions.

There have been many reports of adhesives causing reactions although very few reports of systemic reactions from adhesives. Many adhesive materials contain natural rubber latex. Finally, there have been reactions associated with exposure to latex via latex stoppers. There are hundreds of other sources of latex that have been listed, but all in relatively small numbers.

As was indicated before, part of the problem with latex allergy and the reason it seems to have followed the time course that it has, has been associated with the dramatic increase in latex glove sales worldwide, and this is from no less a medical and statistical source than USA Today, in March 1994, which shows nicely and graphically the increase, and this is in billions of gloves that were sold in the United States, going from 1.4 billion in 1988 up to very high numbers within a few years.

This was associated with universal precautions and has certainly been implicated in a number of sources as certainly an association and possibly causative of the latex allergy that we have witnessed.

Now, latex allergy can occur in the general population, and we will talk about this in a few slides, but you are also going to hear throughout the day today about specific risk groups that seem to be more likely than the general population to develop latex allergy.

I really want to preface what I am going to say about this in saying that there is actually considerable controversy about this, and I am going to try to present the balance to you of the controversy.

But it was clear from initial reports, from all of the initial reports, that there seemed to be a greater likelihood of this happening in certain groups, and the group that I studied back in the early 1990s was the group that had meningomyelocele or spina bifida, and children with urogenital abnormalities, all of whom underwent multiple courses of surgery and

again from many medical centers, mainly pediatric medical centers seem to be at fairly high risk of Type 1 latex allergy.

Other groups that unlike myself, were not pediatricians, but took care of adults, seemed to focus mostly on healthcare workers who appeared with latex allergy, and, in addition, there were some reports of rubber industry workers being at increased risk, as well.

So, the first question is why latex and what is it about latex that seems to elicit these kinds of reactions. Well, the answer is that latex is a natural product. It actually been discovered by the native populations of South and Central America a long time ago, was used largely for recreational purposes and sometimes to provide wound dressings, but the widespread use of natural rubber latex really didn't develop until the 19th century when Dr. Goodyear discovered that by a process of vulcanization, which is heating latex in the presence of sulfur, you could make a product that really was thermally stable.

The British, when they first got to the New World instantly saw a use for the latex that they saw the natives getting out of the trees, and the dipped cloth into this latex material and sent it home and voila, raincoats. The problem was that when the latex got to the temperatures in northern Europe, the latex actually flaked and was highly brittle and wasn't particularly useful.

So, what Dr. Goodyear discovered was a way of turning this natural product into something that was stable and had properties that were of great use.

The Europeans, mainly the British, invested considerable effort to getting the latex plants out of the New World and into the Old World, as they did with many of the plants that they found in the New World, and Kensington Gardens in London basically originated as a place to take New World plants and try and grow them in the Old World.

This met with no success when they tried to export these plants to Europe, but they did have success in setting up plantations in North Africa, and these plantations have names like Goodyear and Firestone, and latex is now grown in these essentially huge biofactories that consist of the latex trees, which are called Hevea brasiliensis.

The latex is harvested by scoring the tree with a sharp implement, placing a spout at the bottom of that score, and then placing a cup under the spout. The workers go out in the pre-dawn hours, they will score the tree, put the cup in place, take a break, and come back and collect the ounces of latex from each tree. It is actually incredibly labor-intensive work.

The plantations actually have their own latex manufacturing plants usually on location.

Here is just a diagram of the bark of the latex tree. This is the outer bark. It shows these transverse vessels in which the latex is transported to the surface. Latex is actually not a sap, it's a common misnomer. Sap, as we know from maple trees, is an extracellular product that contains sugars and relatively little else.

Latex is an intracellular product that is very rich in nucleic acids, fats, as well as proteins, and it actually has an organelle structure to it of which the essential function unit is the rubber particle, which is about the size of a human red cell.

This rubber particle contains, in its interior, pure cis-1-4-polyisoprene. That is the hydrocarbon polymer that we all want and that we all use, but in addition, the rubber particle is coated with multiple proteins, and there are other multiple proteins that are present in latex as it comes out of the tree.

Another important thing to realize is that latex gloves are dipped products. It was realized fairly early on that not all things made out of natural rubber latex had the ability to elicit allergic reactions with equal likelihood.

For instance, we all know why Goodyear and Firestone have latex plantations. They are making tires. **It's relatively uncommon to find somebody who works in an auto shop who has latex allergy or who works in a tire place who has latex allergy.**

It has happened, but when it has happened to me, I have always been able to associate it with a medical exposure to latex gloves. **Latex gloves belong to a class of latex products that are dipped products. The tires are molded products. <u>In general, what has been found just by association is that the dipped products seem to elicit reactions much more likely.</u> That includes condoms, balloons, and lots of other devices.**

Presumably, the reason for this is that the temperatures that the latex is exposed to are considerably lower in the dipping process. It also may have something to do with the surface area of the product itself and simply the exposure of proteins to the surface.

There are specific allergens that have been identified, many specific allergens. This is up to date as of last month when I updated a review article. For those of you that aren't familiar with the allergy nomenclature, the standard allergen nomenclature is to take the first three letters of the genus name of the source material, the first letter of the species name, and

then you have a serial number 1, 2, 3, that is an arabic numeral, which is assigned by the committee that accepts the names for these.

So, latex trees are Hevea brasiliensis, hence, the first latex allergen described is called Hev b 1, which was known as rubber elongation factor. There probably are even more latex allergens that have not yet been described.

One of the things that really was learned fairly early on, and key in the science involved in this, is Dr. Tomazac here from CDRH, who will be talking to you later in the program today, **is a glove powder seems to be an important vehicle for the dissemination of latex proteins.**

Gloves needed to be powdered in order to lubricate them. If you take a latex glove that hasn't been specially treated in some way, or powdered, and you try and pull it on your hand, you just can't do it. Just sort of imagine, you know, kids trying to pull on a bathing suit that is slightly wet, it just won't slide on the skin.

Powdering latex gloves with powder is a form of lubricant. In the bad old days, that lubricant was talc. When the surgeons discovered that it was bad to get talc into a surgical site, it was switched to cornstarch, which is highly absorbable. But glove powder clear absorbs latex antigens and disseminates the antigen proteins on the surface of the powder.

But if you want to look at what the data are that were exposed to specific allergens, it is actually quite easy. **There are only two allergens that I was able to find any evidence that these allergens existed in commercial products**.

The first was **Hev b 1**, in which there is really a wealth of data from mattresses, certainly from gloves, but also a breathing zone analyses of individuals as they go through their work day.

So there is really very solid evidence that people are exposed to Hev b 1 probably in relatively large amounts. There is also evidence that people are exposed to **Hev b 5** through latex gloves, but I was unable to find any evidence of any other of these other allergens. This doesn't mean that people are not exposed. It just means that it hasn't really been sorted out yet.

Latex avoidance is hard for several reasons. It is hard because latex ubiquitous in the healthcare environment. Labeling in the past had been erratic. That has definitely improved dramatically through the efforts of CDRH.

But the other problem that we are facing is that threshold doses are really unknown both for sensitization and for reactivity. The final reason that latex allergen avoidance is hard is that there is this problem of cross-reactivity with foods, which I felt would be of special interest to this committee, so I thought I would spend a couple of slides just talking about this.

Really going fairly far back into the clinical reports of latex allergy were reports of individuals who were reactive both to latex and to certain fruits. The first reports were to banana, avocado, chestnut, and if you look, it is a laundry list of basically all fruit products.

There is clearly a well-documented pattern of cross-reactivity between fruits and certain pollens that is highly specific, but this was a little hard to sort out clinically, but since then, there were a number of immunochemical studies that clearly showed that there was, in fact, true cross-reactivity through inhibition.

Even sequencing studies have gone along with the idea that there is cross-reactivity between latex allergens and other allergens that one might encounter in a variety of food products. Hev b 3 has strong heat sequence homology with a protein from red kidney beans, Hev b 5 with kiwi, Hev b 6 with wheat germ agglutinin, Hev b 7 is a form of potaten, which is a storage protein in potato, Hev b 8 is a profilin. This is a ubiquitous class of proteins in the plant kingdom. Hev b 9 is an enolase and has strong cross-reactivity with fungal enolases, Hev b 10 is a superoxide dismutase likewise, and the lysozymes that have been identified in latex are also ubiquitous proteins.

Main ingredients in the manufacturing of 100% Pure Natural Dunlop Latex: 1. 90-95% natural rubber, 2-3% zinc oxide, 1-2% fatty acid soaps, 1-2% sulphur, and 1-2% sodium. The last 4 items are necessary in the vulcanization, foaming, and curing process. Most of this is baked out. The finished core is then washed a minimum of 3 times. The finished product is approximately 99% natural rubber.

Source – EcoChoices