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REVIEW

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A Current Overview of Latex Allergy

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ABSTRACT

Latex allergy is a disease with increasing prevalence and importance and can be seen in the whole population, especially in healthcare workers and those working in rubber production. It can lead to clinical pictures ranging from allergic urticaria to dermatitis, rhinoconjunctivitis, asthma, and even anaphylaxis. Various methods are used for the diagnosis, including the skin prick and patch tests, latex-specific immunoglobulin E, and nasal provocation. Latex fruit syndromes may also occur due to cross-reactivity with latex.

Preventive measures and patient education constitute the most important part of the treatment. Medication, latex immunotherapy, and the use of omalizumab are among the main treatment modalities.

Keywords: Latex allergy, Hevea brasiliensis, anaphylaxis, immunotherapy, omalizumab

Abbreviations: **NRL:** Natural rubber latex, **IT:** Immunotherapy, **IgE:** Immunoglobulin E, **SCIT:** Subcutaneous immunotherapy, **SLIT:** Sublingual immunotherapy.

INTRODUCTION

Latex is produced by the lactiferous cells of the rubber tree Hevea brasiliensis (1). It grows in the tropical climate zone. It is native to West Africa, South Asia, and America. Natural latex is processed and many chemicals are added to it, turning it into a very durable and flexible material. Today, latex is widely available in many products. Its use is increasing, especially in the field of health. Latex was first used in the medical field in surgical gloves in 1984 by Richard Cook. However, the surgical use of latex gloves was popularized by William Halstead (2).

Since the 1980s, it has been shown to prevent the transmission of viruses such as blood-derived Human Immune Deficiency (HIV), Hepatitis B (HBV), and Hepatitis C (HCV), and its use has become increasingly widespread (3,4). Latex production from Hevea brasiliensis is shown in Figure 1.

Figure 1. Obtaining latex from Hevea brasiliensis (www.immune.com/rubber/nr1.html).

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Latex allergy is increasing day by day among the population. It ranks second after neuromuscular blocking agents among the causes of intraoperative anaphylaxis in patients who have undergone surgery (5). Hospital personnel working in the operating room and intensive care unit come into contact with the allergen through the respiratory tract due to the presence of powdered latex glove proteins in the air, and/or through the skin as a result of contact with medical materials such as catheters and probes made of latex. As a result, a series of clinical findings extending to contact dermatitis, urticaria, allergic rhinitis, asthma, and even anaphylaxis occur (6,7).

The prevalence of latex sensitivity in the general population is <1% to 7.6% (8) The prevalence in those who are frequently exposed to natural rubber latex (NRL) is between 3% and 64% (8). The prevalence was found to be 30% in dentists, 50% in surgeons, 25% to 50% in nurses, and 15% in the remaining healthcare personnel (9). Latex sensitivity is more prevalent in individuals who have undergone more than five procedures (10). Those with neurological conditions including cerebral palsy and spina bifida, as well as those with other congenital defects such gastroschisis, omphalocele, and esophageal atresia, may have a greater frequency of latex allergy (11). A history of atopy and exposure to latex-derived items through skin contact or inhalation during surgery are two of the many risk factors for developing NRL allergy in medical staff and patients (10-12).

EXAMPLES OF PRODUCTS CONTAINING LATEX (13).

a. Medical supplies

Gloves, cervical dilator, tourniquet, nasogastric tube, stethoscope, urinary catheter, syringe, endotracheal tube, electrode pads, drains, catheters, surgical masks, hemodialyzer, infusion set, anesthesia masks, airway, air mattresses, dental prostheses, the rubber of some medicine bottle covers.

b. Office products

Tapes, eraser, telephone cables, computer mouse pads.

c. Home supplies

Washing gloves, toys, bath curtains, teats, sponges, balloons, condoms.

d. Other

Car wheel, helmet, marine mattresses, rubber foot pumps, shoe soles

RISK FACTORS FOR LATEX ALLERGY (2,4)

1. Health workers
2. Latex wood industry workers
3. Individuals who have had latex-containing medical devices applied to the mucous membranes at an early age (people with spina bifida or urogenital anomalies)
4. Persons who have undergone repeated or prolonged surgical procedures
5. Atopic people
6. People with food allergies (cross-reactive proteins, especially banana, avocado, chestnut, kiwi, melon, tomato)

Allergenic proteins of NRL and their characteristics are shown in Table I (1,2,6)

Of the 250 different NRL polypeptides identified, 60 could bind to human IgE antibodies. Only 15 of the allergens identified by the International Nomenclature Committee of Allergens in the International Union of Immunological Societies (IUIS) Committee have been given official numbers. Hev b 1, 2, 3, 4, 5, 6.02, 7.01, and 13 have the highest allergenicity (14-16). There is uncertainty in the clinical significance of certain Hevea allergens, such as Hev b 2 and Hev b 13.

Hevea indicator allergens: The four Hevea proteins are considered "indicator" allergens in the assessment of the allergen content of rubber products and are useful as markers of latex presence in the environment (Hev b 1, Hev b 3, Hev b 6.01/6,02) (17,18). Hev b 1 (rubber elongation factor), and Hev b 3 (prenyl transferase) are associated with the surface of the polyisoprene rubber particle. They are more difficult to aerosolize and therefore sensitization to Hev b 1 and 3 requires direct mucosal contact with Hevea rubber products, as may occur during surgery. Hev b 5 (acidic protein) and Hev b 6.01/6.02 (mature hevein) are soluble allergens found in latex cytosol or C serum Hev b 5, and 6.01/6.02 are the main allergens that play a role in the sensitization of healthcare workers. These allergens are aerosolized in to the environment during the wearing of powdered latex gloves (19) and exposure to these allergens can also be through direct contact.

CLINICAL SYMPTOMS

Type I hypersensitivity responses to latex present clinically in a wide range of ways depending on the mode of exposure (cutaneous, percutaneous, mucosal, or parenteral), the number and kind of allergens, the level of sensitivity, and individual variables (11).

Skin symptoms

As a type I hypersensitivity reaction driven by latex-specific immunoglobulin E, immunological contact urticaria develops in previously exposed people (IgE). There is debate over protein contact dermatitis (19). A mix of immediate-type (type I) and delayed-type (type IV) hypersensitivity is likely how it is described (20,21). Clinically, it appears as chronic eczema that is marked by repeated flare-ups of acute pruritic, occasionally vesicular, eczema at the contact site. The processing of latex rubber with additives, such as 1,3-diphenyl guanidine, can also result in allergic contact dermatitis (type IV hypersensitivity) (22).

Respiratory symptoms

Contact with latex particles absorbed by the cornstarch used in latex gloves results in respiratory symptoms such as rhinitis, conjunctivitis, cough, and asthma (23). Latex-induced eosinophilic bronchitis is a rare occupational respiratory disease (24).

Systemic reactions

While performing medical or surgical procedures such as surgery, gynecological operations, or dental exams, anaphylactic responses (25) typically result from mucosal contact (11). The most typical clinical picture in patients receiving anesthesia is cardiovascular collapse; however, skin rashes and bronchospasm are also frequent. Latex reactions normally occur during the maintenance phase of anesthesia (24).

Clinical manifestations of latex allergy are shown in Table II (26,27).

LATEX FRUIT SYNDROME

Latex and banana-related allergy was described in 1991 (28) and latex, avocado, and banana-related allergy in 1992 (29). Latex fruit-related allergy was also defined in the same year (30). Latex chestnut hypersensitivity was detected in 1993 (31,32). Due to a cross-reaction with food allergens, latex fruit syndrome is reported to affect 40% of people with latex allergies (mainly banana, avocado, chestnut and kiwi). Allergic reactions to Hev b 2, Hev b 6.02, Hev b 7, Hev b 8, and Hev b 12 have reportedly caused this

Table I: Allergenic proteins of NRL and their characteristics (1,2,6).

Allergen	Name	Associated clinic	Literature
Hev b 1	(Rubber Elongation Factor)	Patients with spina bifida	Chen et al., 1997
Hev b 2	(β-1,3-glucanase)	Adult latex allergic patients	Yagami et al., 2002
Hev b 3	(microhelix component)	Patients with spina bifida	Wagner et al., 1999
Hev b 4	(lesitinase homologue)		Bernstein et al., 2003
Hev b 5	(acidic protein)	Patients with spina bifida	Statrter et al., 2006
Hev b 6	(prohevein)	Patients with spina bifida	Bernstein et al., 2003
Hev b 7	(patatin analogue)		Bernstein et al., 2003
Hev b 8	(profilin)		Nieto et al., 2002
Hev b 9	(enolase)		Wagner et al., 2000
Hev b 10	(Mn-superoxide dismutase)		Rihs et al., 2001
Hev b 11	(class 1 chitinase)	Allergenicity not defined	
Hev b 12	(lipid transfer protein)		Beezhold et al., 2003
Hev b 13	(esterase)		Bernstein et al., 2003
Hev b 14	(hevamine)	Allergenicity not defined	
Hev b 15	(Serine protease inhibitor)	Hans-Peter Rihs	2014

Modified from Allergen nomenclature. Available from: http://www.allergen.org/search.php?allergensource=latex

condition (33). Class 1 chitinases (Hev b 6) are crucial for the condition known as the latex fruit syndrome, which affects 21 to 58% of those who are allergic to latex (34,35). Hev b 6 exhibits homology with chitinases found in fruits including bananas, avocados, and chestnuts, and they have a protective role. The latex fruit syndrome may be caused by other latex allergens such as profilin, glucanases, and nonspecific lipid transfer proteins (ns-LTPs). Curry spice and cassava (Manihot esculenta) have both been observed to cross-react with meals containing latex, and these responses are considered to be connected to sensitivity to Hev b 5 (a protein of uncertain function) and Hev b 8 (profilin), respectively. There have been reports of cross responses to tomato and potato, which have been linked to sensitivity to Hev b 7, a patatin-like protein. Furthermore, cross-reactivity between bell pepper lascorbate peroxidase and Hev b 2, a beta-1,3-glucanase has been documented (34).

When Hevea latex is centrifuged, it separates into 3 layers (36,37). The top layer contains NLR particles (27%) rich in Hev b 1 and 3. In the middle, serum C (latex cytosol; 48%) contains Hev b 5, 7, 8 and 9, including plant enzymes. The substrate contains lutoid (B-serum; 30%) composed of luciferous organelles containing hevamines with chitinase and lysozyme activity, and hevein, a fungitoxic protein. Hev b 2, 4, 6.01/6.02, 7, 10, 11 and 13 are found in this layer. Both B and C serum proteins are water-soluble and a mixture of B and C serum proteins was used to prepare the diagnostic skin test solutions.

Milky liquid or latex from rubber tree is processed in one of two ways (11). 90% of Hevea latex is coagulated, molded and used in the manufacture of rubber products such as pneumatic tires for vehicles and airplanes, syringe plungers, bottle stoppers and shoe soles. As a result of this process, solid rubber products contain low levels of latex allergens, primarily Hev b 1 and Hev b 3.

The remaining 10% of Hevea latex is ammoniated to prevent bacterial growth. Various low molecular weight chemical additives such as antioxidants, accelerators, and preservatives are often used in the process. Ammoniated latex is used to manufacture rubber products such as medical gloves, condoms, catheters, and toy balloons dipped in porcelain molds. Dipped rubber products contain higher levels of latex allergens, including Hev b 5, Hev b 6 and Hev b 13. Most allergic reactions to Hevea latex proteins are the result of exposure to dipped rubber products. Total extractable latex protein is significantly reduced in commercially produced latex gloves by treatment with natural proteases such as papain and bromelain after dipping (38). It was found that 50% of commercial latex gloves tested retained levels of allergenic latex protein between 215 and 1308 mcg/g in a 2016 study (39).

DIAGNOSIS OF LATEX ALLERGY

Skin tests

Extracts prepared with Hevea latex B and C serum proteins and standardized for their allergen content and stability are used (40,41)

Skin testing involves puncturing the medial surface of the forearm with a lancet device by instilling a drop of latex extract at sequential concentrations ranging from 0.001 to 1 mg/mL of protein. Results are read after 15-20 minutes and compared to positive histamine and negative saline controls. Care should be taken when performing skin testing with a latex extract, as there has been a report of anaphylaxis triggered by a skin prick test with latex (42).

In pediatric patients with a history of urticaria, rhinoconjunctivitis, and/or asthma suspected to be triggered by NRL allergy, the sensitivity ranged from 65 to 96% and specificity from 88 to 94% with the use of available extract products (43).

Table II: Clinical manifestations in latex allergy (26,27).

Latex Allergy Symptoms
• Nonimmune reactions (irritant contact dermatitis): These develop slowly and can last for days; they occur usually with hand washing; antiseptics, gloves, and chemicals are the cause. Symptoms; redness, rhagades, fissures, and crusts are formed.
• Type IV (Delayed type cell-mediated hypersensitivity): Begins 48 hours after contact, symptoms include erythema, cysts, papules, pruritus, vesicles, and crusting.
• Type 1 (Early type IgE-mediated hypersensitivity): Onset within minutes, very rarely exceeding 2 hours. Symptoms; urticaria, angioedema, nausea, vomiting, abdominal cramps, rhinoconjunctivitis, bronchospasm, fainting and anaphylactic shock.

Serological tests

Hevea latex specific IgE antibody is measured in serum to confirm sensitivity when skin test reagents are not available (44-46). There are two serological methods commonly used all over the world: ImmunoCAP and Immulite autoanalyzers (46,47). When ImmunoCAP and Immulite tests are compared with the skin puncture test, the sensitivity in diagnosis is 70% and above, and the specificity is >95%. The detectable lower limit of these serological tests is 0.35 kUa/L (48,49). A chip-based microarray containing eight recombinant Hev b allergens has been shown to clearly define the specificity of anti-latex IgE without loss of diagnostic sensitivity compared to singleplex ImmunoCAP (50).

When skin test positive patients with latex allergy were evaluated, the diagnostic sensitivity of ImmunoCAP-ISAC in detecting IgE antibody against at least one Hev b allergen was found to be low (55%) (49). ImmunoCAP-ISAC is important in detecting susceptible but asymptomatic individuals with IgE positivity caused by the cross-reactive latex profilin (Hev b 8) (51).

Provocation tests

Many of these methods are not suitable for routine clinical use and are used for research purposes. They are seen as a last resort when all other tests are negative and the patient's history is strongly suggestive of latex sensitivity. There are various types such as the use of gloves, nasal provocation, and inhalation provocation tests. Latex-related skin reactions or upper and lower respiratory tract allergic symptoms are accepted as the end point of provocation tests (52-54).

Allergy tests for latex-related foods

If a latex-allergic patient has a history of allergies to latex-related foods, the food in question should be avoided and testing for that food is not required. Patients who are unsure whether they tolerate latex-related foods are not routinely evaluated for sensitivity to these foods. However, if a latex-allergic patient also has a history of allergy to latex-related foods, cross-sensitivity should be investigated by performing a skin puncture test with food extracts or fresh food, a food-specific serum IgE test, or an oral challenge test with food. In the absence of a history of positive reactions to latex cross-reactive food, it is recommended not to perform skin or serology testing as this may lead to "positive" IgE antibody results of unknown clinical significance and inappropriate avoidance practices.

LATEX ALLERGY MANAGEMENT

Most patients, such as healthcare workers and workers in latex manufacturing, wear latex gloves or use latex products, e.g. during work or medical interventions, or become sensitized by exposure to dental dams, condoms, and balloons. Avoiding latex products comes first in the management of latex allergy. Many other therapeutic approaches are under investigation, including immunotherapy (IT) and anti IgE therapy. There are four options for preventing or managing allergic symptoms. These are avoidance, IT, pharmacotherapy and anti-IgE therapy. The most effective and least expensive method is avoidance (55-58).

It is possible to treat acute and chronic allergic symptoms with pharmacotherapy. Preventive pharmacotherapy is rarely effective in preventing reactions. The use of IT is limited because adverse reactions are common (56, 59).

Anti-IgE therapy is under investigation for off label use in patients with IgE-mediated latex allergy (60,61). Anti-IgE is sometimes used in conjunction with an immunotherapy regimen. However, it is expensive and patients need an appropriate body weight and serum IgE levels between 30 and 1500 kU/L for omalizumab treatment.

Individual strategies

Patients diagnosed with latex allergy should avoid contact of latex allergens with the skin, mucous membranes, and respiratory tract. In addition, latex-sensitive patients may experience life-threatening anaphylaxis upon incidental contact with latex allergens, and should be prescribed an adrenaline autoinjector and instructed in its use. The patients must be educated about the transmission of latex allergens via the air and when inhaled. Patients should be aware of the fact that some rubber products contain a lubricating powder that carries latex proteins to the air or dust, and may cause an allergic reaction (62).

Various precautions are recommended for people with latex allergy to prevent allergic reactions (4,63):

1. A medical alert bracelet indicating a latex allergy should be worn.
2. An adrenaline auto injector should be prescribed to all individuals with a history of systemic reactions to latex.

3. Nonlatex gloves should be used.
4. Allergies must be reported prior to any medical, dental, gynecological, or surgical procedure and a latex-safe environment should be provided in response (64).

Education

Latex is not an occupational allergy that only affects healthcare workers. It is an allergen that has the potential to cause allergic symptoms in people sharing the same environment (65). The best practice to be protected from latex allergy is to educate the risk groups (66). There are numerous publications on the importance of avoiding latex allergens. After avoiding the use of powdered latex gloves, there has been a significant reduction in sensitization (67).

There are two situations that should be particularly noted regarding latex allergic patients in a healthcare setting. The first involves patients with spina bifida: care should be taken not to use any latex products in contact with these individuals from the moment of birth, as there is a risk of hypersensitivity. Second, patients with a latex allergy may need surgery or other special procedures in the operating room. In elective cases, these patients should be treated as the first case of the day and nonlatex gloves should be used (62).

Workplace

A diagnosis of latex allergy needs to be confirmed for a systematic approach to the management of a worker with a suspected NRL allergy (68,69). Confirmation of latex sensitivity is also the first step in preventing further latex exposure at the patient's workplace.

Fifteen IgE antibody measurements specific to Hevea latex allergenic components do not increase the diagnostic sensitivity for latex-induced occupational asthma, compared with detection of IgE antibody against natural extract alone (68). However, IgE anti-latex component measurements help to distinguish between different latex allergen exposure routes, such as inhalation (Hev b 5/6.02) and mucosal (Hev b 1/3).

It should be documented that deterioration and disability resulted from latex exposure in the workplace. The employer then needs to be educated about the patient's diagnosis and responsibility for creating a latex-safe environment. If patients cannot be ensured to work in a suitable environment, employee compensation and rehabilitation may be appropriate.

Schools

A systematic approach to managing a confirmed NRL allergy in a student in a school program begins with the development of an individualized health care plan and a school wide avoidance plan. If the child is at risk of anaphylaxis, education of the student in self-management skills is vital (70).

IMMUNOTHERAPY

Immunotherapy (IT) is used for the treatment of IgE-mediated latex allergy. However, this treatment is limited by the frequency and severity of IT reactions (71). Several small, randomized studies have been conducted with conventional subcutaneous immunotherapy (SCIT) using crude latex extracts (72-74). Efficacy was variable in these studies. One study showed a reduction in symptoms of urticaria and rhinoconjunctivitis but no reduction in asthma symptoms (72), while another showed a reduction in airway hyperreactivity to latex (73). A third trial failed to show any difference in drug use or symptom scores (74). A high frequency of adverse events, including systemic reactions, was reported in all studies. In one study, adverse events occurred with similar frequency in both the induction and maintenance phases of the IT regimen (72).

Some studies suggest a lower frequency and severity of adverse events with sublingual immunotherapy (SLIT) compared with SCIT (75-79). However, outcomes are variable and anaphylaxis has been reported with SLIT (80,83).

New IT approaches are being explored to reduce the risk of serious adverse reactions and still maintain or improve efficacy. These approaches include recombinant allergens, T-cell epitope-based peptides, and adjuvants conjugated to or co-administered with the allergen (84). These treatments are still in the experimental stage.

BIOLOGICAL DRUGS

There is only one study demonstrating that omalizumab, a monoclonal anti-IgE antibody, provides clinically significant ocular and skin anti-allergic effectiveness in healthcare professionals with latex allergy (61). More research is required in order to understand how this treatment is financially beneficial.

CONCLUSIONS

Latex allergy is an increasingly common disease in the population, especially in healthcare staff and workers in the latex industry.

Skin tests, serological tests, and provocation tests are used for diagnosis.

The condition causes clinical pictures ranging from urticaria, dermatitis, rhinoconjunctivitis, and asthma to anaphylaxis.

Prevention comes first in the treatment. It is used when necessary in medical procedures. Although there are treatment options with immunotherapy and biological agents, these are controversial.

Conflict of Interest

The author declares that there is no conflict of interest in the preparation and publication of this article.

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Author Contributions

Concept, design, data collection and processing, analysis or interpretation, literature review, writing, approval: **Feridun Gurlek.**

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