LATEX ALLERGY

Gulko SV[1], Babadjanova GYu[1,2]✉

[1] Lomonosov Moscow State University, Ministry of Education and Science of the Russian Federation, Moscow, Russia

[2] Pulmonology Research Institute, Federal Medical Biological Agency, Moscow, Russia

Latex, made from *Hevea brasiliensis sap*, is the material used to make many medical products, including catheters, balloons and gloves. Hundreds of allergens from natural rubber latex have been identified, and 15 of them were numbered, from Hev b1 to Hev b15. Natural proteins in rubber cause both asymptomatic sensitization and type I IgE-mediated hypersensitivity. Treatment of latex makes use of chemical antioxidants that can also bring about type IV hypersensitivity reactions. Latex allergy is one of the most common causes of anaphylaxis in the operating room, and its prevalence has been growing since 1980s, together with the popularity of latex gloves. It is a well-known problem among medical professionals, with gloves and inhaled aerosol particles being the sources thereof. This study aimed to review the current scientific research and practical data in this only partially investigated area. In addition, increasing the awareness of doctors and patients minimizes the existing risks of latex allergy.

Keywords: latex allergy, latex, latex anaphylaxis, rubber, type I hypersensitivity

Author contribution: Gulko SV — literature search and article formalization; Babadjanova GYu — management, editing, commenting.

✉ **Correspondence should be addressed:** Goulnara Y. Babadjanova
Orekhovy bul'var, 28, 115682, Moscow, Russia; babadjanova@rambler.ru

Received: 08.11.2023 **Accepted:** 15.12.2023 **Published online:** 31.12.2023

DOI: 10.47183/mes.2023.064

АЛЛЕРГИЯ НА ЛАТЕКС

С. В. Гулько[1], Г. Ю. Бабаджанова[1,2]✉

[1] Московский государственный университет имени М. В. Ломоносова Министерства образования России, Москва, Россия

[2] Научно-исследовательский институт пульмонологии Федерального медико-биологического агентства, Москва, Россия

Латекс, получаемый из сока каучукового дерева *Hevea brasiliensis*, используют для изготовления многих медицинских изделий, включая катетеры, баллоны и перчатки. Были идентифицированы сотни аллергенов из натурального каучукового латекса, 15 из которых присвоены официальные номера (от Hev b1 до Hev b15). Природные белки в каучуке связаны как с бессимптомной сенсибилизацией, так и с IgE-опосредованной гиперчувствительностью I типа. При обработке латекса добавляют химические антиоксиданты, которые также могут вызывать реакции гиперчувствительности IV типа. Аллергия на латекс — одна из наиболее частых причин анафилаксии в операционной, и ее распространенность возросла с увеличением использования латексных перчаток начиная с 1980-х гг. Она стала широко известной проблемой среди медицинских работников при ношении перчаток и вдыхании аэрозольных частиц. Цель настоящего обзора — изучение актуальных научных исследований и полученных данных в этой пока еще не до конца изученной области. Кроме этого, повышение информированности врачей и пациентов минимизирует имеющиеся риски появления аллергии на латекс.

Ключевые слова: аллергия на латекс, латекс, латексная анафилаксия, резина, гиперчувствительность I типа

Вклад авторов: С. В. Гулько — поиск литературы и оформление работы; Г. Ю. Бабаджанова — руководство, редакция, внесение правок.

✉ **Для корреспонденции:** Гульнара Юсуповна Бабаджанова
Ореховый бульвар, д. 28, г. Москва, 115682, Россия; babadjanova@rambler.ru

Статья получена: 08.11.2023 **Статья принята к печати:** 15.12.2023 **Опубликована онлайн:** 31.12.2023

DOI: 10.47183/mes.2023.064

Polyisoprene, commonly known as natural rubber latex (NRL), is the base of a wide range of commercial products, including medical gloves and aircraft tires. The main source of natural rubber is latex, a juice-like liquid harvested from Hevea brasiliensis (Hev b), a tree growing mainly in Africa and Southeast Asia, especially in Thailand, Indochina, Malaysia, and India [1].

Under the bark of Hevea brasiliensis, there is a network of latex vessels that contains natural rubber, which is a compound of polymer hydrocarbon 1,4-cis-polyisoprene, water, cytoplasmic organelles, and several enzymes and structural proteins involved in biosynthesis of polyisoprene, latex coagulation, and protection of plants from microbes. Some of these proteins are strong allergens that can trigger sensitization and allergic reactions at initial exposure and production of human immunoglobulin E (IgE), provoking a number of allergic reactions, upon subsequent exposure [2, 3].

The purpose of this review is to study scientific papers covering latex and analyze the data on latex allergy.

Terminology

The word "latex" can have several definitions. In the context of this review, it refers to a natural polyisoprene substance, a milky or white liquid. It is produced by the cells of various seed plants, such as milkweed and poppy. This liquid is a source of natural rubber, gutta-percha, chicle, and gutta-balata, widely used in medicine. In addition, the term "latex" may refer to an aqueous emulsion of synthetic polyisoprene, nitrile, neoprene or plastic, products of polymerization. This type of latex is used in production of coatings, adhesives, medical gloves, etc.

Hevea latex allergens

There are about 250 different types of NRL polypeptides, and 60 of them can bind to human IgE antibodies. Fifteen key allergens of those 60 were given official numbers (from Hev b 1 to Hev b 15) by the Committee on International Allergen Nomenclature of

Table. Latex allergens from Hevea brasiliensis

Name	Description	Weight (kDa)	Family	Cross reaction
Hev b 1*	Rubber elongation factor	58/14.6	–	Papain, figs
Hev b 2	Beta 1/3 glucanase	34–36	PR-2	–
Hev b 3*	Prenyl transferase	24–27	–	–
Hev b 4	Microhelix	110/115	–	–
Hev b 5*	Acidic protein	16	–	Kiwi
Hev b 6.01	Hevein preprotein (prohevein)	20	PR-3	Avocado, banana, chestnut
Hev b 6.02*	Hevein protein (mature hevein)	4.7	PR-3	Avocado, banana, chestnut
Hev b 6.03	C-terminal fragment of hevein	15.3	PR-3	Avocado, banana, chestnut
Hev b 7	Patatin homologue (Hev b 7.01/7.02)	43–46	–	Potato (patatin Sol t 1)
Hev b 8	Hevea profilinus	14–14.2	Профилин	Pollen, celery
Hev b 9	Hevea enolase	51	–	Mould
Hev b 10	Mn superoxide dismutase	22–26	–	Mould
Hev b 11	Class I chitinase	33	PR-3	Banana, avocado
Hev b 12	Lipid transfer protein	9.4	PR-14	Peach and other stone fruits
Hev b13	Esterase	42	–	–
Hev b 14	Chitinase, glycosidase hydrolases family 18	30.2	–	–
Hev b 15	Serine protease inhibitor	8	PR-6	Wheat
Hev b CitBP	Citrate-binding protein	27	–	–
Hev b CyP	Cyclophilin-rotamase	18	–	–
Hev b GADPH	Glyceraldehyde-3-phosphate dehydrogenase	37	–	–
Hev b HSP80	Chaperone protein	80	–	–
Hev b IFR	Isoflavone reductase	35	–	–
Hev b PRS	Proteasome subunit	2	–	–
Hev b TRX	Thioredocine oxidoreductase	12	–	–
Hev b UDPGP	Uridine diphosphate-glucose-pyrophosphorylase	52	–	–

Note: pathogenesis-associated protein; Sol t: *solanum tuberosum*. * — "Indicator" proteins, used to assess allergen content in rubber products or as markers of environmental pollution.

the International Union of Immunological Societies (IUIS) [4, 5]. Hevea's 15 allergen proteins have a wide range of applications: rubber biosynthesis, plant protection (from diseases), structure and housekeeping. In addition, there were identified 9 other Hevea proteins that can trigger secretion of IgE antibodies (Table).

The most sensitizing Hevea allergens are Hev b 1, 2, 3, 4, 5, 6.02, 7.01, and 13 [4, 5]. Clinical importance of some of them (Hev b 2and Hev b 13) is still a debated matter, but this discussion is mostly academic in nature, since treatment of latex allergy involves removal of all Hev b allergens from the immediate environment of the patient.

Hevea indicator allergens

The table describes four hevea proteins that can be used as "indicator" allergens in the context of assessment of the content of allergens in rubber products or detection of latex in the environment [6]. Two of these allergens, Hev b 1 (rubber elongation factor) and Hev b 3 (prenyltransferase), are found on the surface of polyisoprene rubber particles; to trigger sensitization, they need to directly contact mucous membrane. Hev b 5 (acidic protein) and Hev b 6.01/6.02 (mature hevein) allergens are soluble, they are part of latex cytosol or serum C. In most cases, these allergens are released by impregnated rubber products, especially latex gloves, and transferred through the aerosol powder used to put on gloves, or pollute the environment. Medical professionals are exposed mainly to the above proteins.

Latex, fruit, and pollen cross sensitization

Polyvalent latex allergy implies a combination of sensitivity to latex and certain fresh fruits and vegetable products. This variety of the condition affects from 30 to 50% of people suffering from latex allergy [7]. The respective allergic reactions can be severe, with up to 50% of such triggered by food being anaphylactic. The food containing allergens associated with latex are bananas, kiwi, avocado, chestnut, papaya, white potato, and tomatoes; the structural homology of the allergens in them is similar to that of Hev b allergens in latex (Table). The main pan-allergen behind cross-reactivity of fruits and latex is a protective protein, class 1 chitinase, which is structurally homological to Hev b 6.01. Hev b 5 is homological with acidic protein of kiwi, peach, and apricot, and Hev b 6.02 — with agglutinin and endochitinase of the wheat germ in avocado and banana. Hev b 7.01 and Hev b 7.02 are esterases structurally homological with patanine patatin (Sol t 1), the main storage protein in potato. Hev b 8 is a profilin promoting cross reactivity with other highly sensitizing profilins of trees, herbs, pollen of weeds, and food [8–10].

Hevea latex treatment

Centrifugation can separate NRL into three layers [1], with the topmost containing natural rubber particles insoluble in water and having a high content of Hev b 1 and 3, the middle layer, or serum C, containing soluble proteins and plant enzymes, including Hev b 5, 7, 8 and 9, and the lower layer — a

precipitate, or serum B, consisting of heveamines, hevein, and other proteins with chitinase and lysozyme activity. This fraction has high content of Hev b 2, 4, 6.01/6.02, 7, 10, 11 and 13. Serum B and C proteins are water-soluble; they are used in production of diagnostic extracts of skin tests.

There are two approaches to treatment of NRL [11]. Approximately 90% of NRL are acid coagulated and used as base for molded rubber products: tires, plungers for syringes, and shoe soles. This process makes the items less allergenic. The remaining 10% are ammoniated and turned into rubber products: gloves, catheters, and balloons. These items have high content of latex allergens, including Hev b 5, Hev b 6 and Hev b 13. They are the key cause of allergic reactions to NRL proteins. Current latex gloves production technology involves treatment with protease, which decreases the levels of extractable latex protein in them, but a certain amount of allergenic proteins remains. Powder free latex gloves usually have the lowest content of allergens because they are washed with chlorine.

Epidemiology

In the mid-to-late 1990s, latex gloves of natural rubber caused a spike of latex allergies among medical professionals who used them. Subsequently, powdered latex gloves were largely refused, which pushed down the number of latex allergy cases among medical staff and patients who had several operations [12]. However, such gloves and other natural rubber products, such as urinary catheters, are still used in some countries, which supports urgency of the latex allergy problem there. Florists, food vendors, and patients, such as those on dialysis, are also at risk of developing allergies [13].

In North America and Europe, there were several factors that caused the latex allergy epidemic. In 1992, the U.S. Occupational Safety and Health Administration (OSHA) issued the Bloodborne Pathogens Standard, which prescribed using protective gloves [12] and also added medical gloves to the list of "universal precautions." Thereafter, the technology was changed to quick processing of latex instead of long storage, which minimized the degree of protein denaturation that naturally occurs during such storage. Thus, the amount of allergenic protein in raw materials and finished medical gloves increased, exacerbating the problem of latex allergy among the medical community [12, 14, 15].

Prevalence in the general population

Prevalence of latex allergy varies depending on the size of the population and techniques used to identify new cases. Skin tests and serological methods are designed to detect Hev b 6.02, the most common allergen in latex extracts [16]. In the mid 1990s, between 3 and 9.5% of the general population had IgE antibodies to NRL. However, as NRL was increasingly removed from the production process, the prevalence of latex sensitization decreased to < 1% by 2006. Clinical allergy is even less common, but the respective indicators disregard patients with non-IgE-mediated allergic contact dermatitis [7].

Prevalence among medical professionals

Latex allergy became a serious health problem in the late 1980s, especially among medical professionals who were exposed to hevea allergens via powdered latex gloves, which means both direct skin contact with them and inhalation of aerosols thereof [17]. By the mid-1990s, the prevalence of sensitization to hevea allergens in the medical community was at 12.1%, but with the introduction of powder-free gloves, it decreased to 4–7%. However, balloons, latex plates, and rubber dam sheets used in dentistry still cause latex allergy [18].

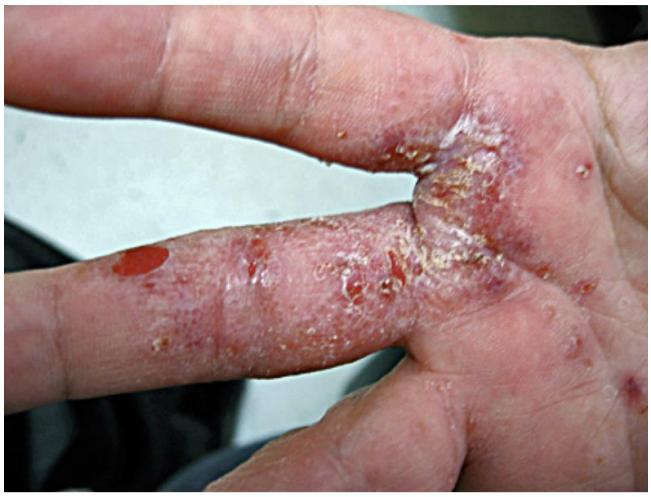

Fig. Contact dermatitis

In Western countries, where natural rubber gloves have been generally abolished, the COVID-19 pandemic weakened state control over the type of gloves ordered. However, in Asia and other regions that have not banned natural rubber gloves on the national level, latex allergy remains an urgent problem [19].

Prevalence of latex allergy among patients who had several operations

Latex sensitization and allergies are common in people who had multiple surgeries, especially on the organs of the abdominal cavity or genitourinary system. Children with spina bifida are considered to be at high risk, as they are often exposed to latex in the context of numerous operations, catheterization of the bladder and manual removal of the rectum. It was estimated that from 1/3 to 2/3 of children who underwent surgery in the 1990s became sensitive to hevea allergens. In some parts of the world, the prevalence of latex allergy in patients with myelomeningocele remains high (19.5%), and more than five surgeries is the most important risk factor for this condition [20].

Risk factors

The main factors that increase the risk of developing latex allergies are professional exposure and atopy. People with eczema or allergies to fruits and vegetables are also more likely to further develop these conditions [21]. Compared to people without atopy, predisposed medical professionals with latex allergies are more likely to have certain polymorphisms of interleukin (IL) promoters, such as IL13 and IL18 [21]. However, in patients with spina bifida or bladder exstrophy and concomitant latex allergy, such polymorphisms were not abnormally frequent. Instead, the risk factors for these patients are the number of previous operations and the history of atopy [22].

Clinical manifestations

The symptoms occurring as part of reaction to latex are shaped by various factors, including method of exposure, amount of allergen present in the natural rubber product, and the main reaction mechanism (irritation, non-IgE-mediated or IgE-mediated) [23].

People wearing medical gloves of hevea latex most often complain of dry, cracked and irritated skin [24]. Erythema

and vesicles are also common. This rash looks like allergic contact dermatitis, but it cannot be attributed to delayed hypersensitivity to additives in gloves. On the contrary, it is an irritant contact dermatitis caused by sweating due to glove occlusion, prolonged contact with alkaline pH medium (made such by corn starch used in many powder gloves), frequent hand washing, and use of aggressive products for this purpose.

Allergic contact dermatitis

Skin rash and itching are common symptoms of allergic contact dermatitis that manifests 1–4 days after contact with a product made of NRL. The rash initially takes form of acute eczematous dermatitis, often with vesicles, then becomes dry, crusted and lichenized. Lichenization (thickening of the skin with emphasized folds or a pattern that looks like deep grooves and wrinkles) is a delayed hypersensitivity (type IVc) mediated by T cells, triggered by oxidizing chemicals and accelerators (thiurams, carbamates, benzothiazoles, thiourea, amines) used in latex production, i.e., it is not a reaction Hev b allergens. However, contact dermatitis may increase the risk of IgE-mediated sensitization to latex due to increased absorption of allergens through skin lesions [25].

Allergic contact urticaria

Allergic contact urticaria or contact dermatitis is an immediate type I hypersensitivity reaction mediated by IgE, manifesting as contact urticaria (Fig.) [26]. This type of reaction is often reported by medical professionals using latex medical gloves. Within 10–15 minutes of exposure, redness, itching, blisters and rashes may appear.

Rhinoconjunctivitis and asthma

In the process of using powdered latex gloves, hevea allergens are released as haze, which can cause symptoms of rhinitis and asthma in people sensitive to latex [23]. Latex-induced sneezing, itching, lacrimation, nasal congestion and runny nose are similar to the symptoms of seasonal pollen allergy.

A history of asthma is not a mandatory prerequisite for development of latex-induced asthma. Allergic symptoms manifesting in the upper and lower respiratory tract can be so severe that some people who are exposed to latex at work have to quit unless their employer totally removes latex from their environment or significantly limits contact therewith [25, 23].

Anaphylaxis

There are reports of anaphylactic reactions to various latex-containing products, both in medical and non-medical settings [25, 27, 28]. The products that most often cause anaphylaxis are:

- gloves;
- balloon catheters;
- dental cofferdams or latex sheets designed to isolate one or more teeth in the oral cavity during treatment;
- condoms;
- bonding glues for hair extensions;
- toy balls;
- pacifiers, teethers, bottle nipples.

Diagnostics

Diagnosing latex allergies can be difficult. The best way to determine if a person is allergic to latex is to carefully study his medical history, especially what concerns exposure and symptoms. Although skin tests, not yet available in Russia, serology and provocative tests can be used to confirm the diagnosis, they have limitations connected with unavailability of reagents, variable sensitivity and specificity, and possibility of severe reactions.

Medical history

Diagnosing a latex allergy requires a thorough clinical history of allergic reactions associated with exposure to products containing NRL [29]. If the patient shows proves hypersensitive to a product (reaction within minutes after contact), and the suspected cause thereof is NRL, it is necessary to investigate all potential allergens, since the first assumption about NRL may be false. For example, there was reported a case of a life-threatening anaphylactic reaction in a woman allergic to cow's milk immediately after using new kickboxing gloves, and it was later discovered that the trigger was not NRL but casein, a component of cow's milk that is part of the glove filler [30].

Latex allergy is associated with various risk factors: hand dermatitis, allergy to fruits/vegetables, and atopy. If clinical history suggests latex allergy, the next step is testing for sensitization to hevea allergens by either epidermic method or search for hevea-specific IgE in serum. Patch tests (application tests) can help differentiate between cell-mediated delayed hypersensitivity reactions to Hev b latex components and immediate hypersensitivity reactions caused by IgE antibodies in response to chemicals added to rubber [29]. Unfortunately, all these tests are not yet available in Russia.

Objective latex allergy studies

In different countries, there are different recommendations for diagnostic tests used to confirm a latex allergy diagnosis.

Study strategies and available reagents

In the USA, the equipment commonly used to detect NRL-specific IgE antibodies in serum are FDA-approved analyzers. The respective systems (ImmunoCAP, Immulite, etc.) are typically operated by clinical immunology laboratories [31, 32]. If the known reagents are available in a country, the first step may be a skin test (injection or puncture), followed by a search for latex-specific IgE antibodies in serum enabled by an automatic analyzer, if results of the skin test contradict the diagnosis based on the patient's medical history [33, 34].

Skin tests

Extracts of whey proteins B and C from NRL are a reliable and safe base for skin tests designed to detect latex allergy. The effectiveness of this procedure can be improved by standardizing allergen extracts and their stability, as recommended in previous studies [29–32].

In Europe and Canada, a skin puncture test usually employs glycerinated latex extracts of hevea from at least three commercial sources [33]. The extracts are prepared with sterile filtered serum C obtained from non-ammoniated or ammoniated NRL; they are glycerinated to keep them stable and prolong their shelf life. Serum C contains both soluble and lutoid allergens released from rubber particles. The non-ammoniated form of serum C, used in European reagents for skin tests, has an extensive allergenic composition.

Diagnosing a latex allergy involves a skin puncture test and successive concentrations of the NRL extract. However,

there have been reports of cases of anaphylaxis caused by this procedure. The sensitivity and specificity of this test ranged from 65 to 96% and from 88 to 94%, respectively, in children with urticaria, rhinoconjunctivitis and/or asthma, whose history suggested latex allergy [34].

In the USA, there are no commercially available reagents for skin tests, and shop-made NRL extracts differ significantly in the content of allergens. Such non-standard extracts undermine trust in the results of the tests, which can be false-positive, and the testing itself can trigger systemic reactions. Puncturing a hevea-containing item is not recommended, since this technique disallows control over the amount of allergen distributed in the skin, thus posing a threat of a systemic allergic reaction as a result of exposure to high doses, or unintentional inhalation [35].

Serology

In the absence of NRL skin test reagents, the preferred alternative is a latex-specific IgE test [29, 34–36]. There are two widely used solutions therefor, ImmunoCAP and Immulite automated analyzers [36]. Noveos analyzer, approved by the U.S. Food and Drug Administration and used in Europe, remedies the problems associated with interference of anti-CCD IgE and exogenous biotin, which may arise with ImmunoCAP and Immulite, respectively. These tests include incubation of human serum with an allergen-containing NRL reagent, and detection of the bound IgE antibody with a reagent labeled by an anti-IgE enzyme. The reported lower quantification limit of these tests is 0.1 kU/l (0.24 ng/ml). ImmunoCAP and Immulite have diagnostic sensitivity and specificity of approximately 70% and > 95%, respectively [37, 38]. A chip-based micromatrix containing eight recombinant Hev b allergens showed better specificity against anti-latex IgE, but it is more expensive and offers analytical sensitivity inferior to that of single IgE assays [39]. ImmunoCAP ISAC can detect latex allergy and sensitization, and identify sensitized but asymptomatic individuals [40]. However, it has only 55% diagnostic sensitivity for IgE antibodies to at least one Hev b allergen, as applied to patients with latex allergy and positive skin tests.

Provocative tests

There are various provocations that aim to induce skin reactions or respiratory allergic symptoms, including glove, nasal, and inhalation tests [41–45]. However, most of these methods are still considered to belong in the realm of research, i.e., they are not recommended for routine clinical practice.

Detection of cross-reactivity food allergies

Patients with latex allergies who specifically request testing for possible cross-reactivity can be prescribed skin prick tests with food extracts or food-specific IgE tests. However, in such situations, skin test or serology without a previous reaction can return a "positive" result confirming secretion of IgE antibodies, which may have no clinical significance and lead to unnecessary measures designed to prevent contact with the allergen.

Mechanisms of development of latex allergy

Latex allergy can manifest as delayed (type IV) or immediate (type I) reactions. Individuals with delayed hypersensitivity triggering contact dermatitis associated with chemical sensitization by accelerants are more likely to develop IgE-mediated systemic reactions (type I) [37]. Thus, everyone with latex sensitivity confirmed by a positive response of IgE antibodies to NRL should be treated the same way.

Latex allergy prevention and treatment strategies

After a confirmed latex allergy diagnosis, there are four applicable prevention and treatment strategies:

- abstention, the most efficient and cost-effective approach implying prevention of contact with NRL allergens [46–50]. In many regions, the prevalence of latex allergy has dropped significantly among healthcare professionals and population in general, and in some cases, it was rendered undetectable by common measures designed to prevent contact with the allergen. This includes a practical latex-safe (not latex-free) strategy adopted by most general and dental clinics, and retirement homes [49];
- pharmacotherapy, which is applicable against acute and chronic allergic symptoms, but it is preferable to prevent reactions and the possibility of increased sensitization. Unfortunately, preventive pharmacotherapy is usually ineffective;
- immunotherapy (IT), which has limited use due to lack of approved therapeutic NRL extracts and high frequency of adverse reactions associated with experimental extracts [47, 50, 51], which have not been approved to this day;

Anti-IgE therapy, which is currently being studied in the context of latex allergy treatment, with no approval for this purpose so far [52]. In some cases, anti-IgE treatment is combined with IT. However, it is important to note that it can be expensive, and its applicability depends on the patient's body weight and the total serum IgE level, which should be in the range from 30 to 700 kU/l [52, 53].

Rejection of latex in clinics, retirement homes, etc.

Latex-safe environment

Creation of completely NRL-free environment is an unrealistic goal. Instead, effective prevention of latex allergies in healthcare settings was realized through creation of a "safe latex environment," which prioritizes control over the effects of latex allergens on healthcare professionals, population, and people allergic to NRL.

Latex advisory committees

Most medical institutions in the United States have established latex committees and programs aimed at eliminating exposure to NRL allergens [48, 54–56]. Interdisciplinary advisory bodies usually comprise local experts in various fields, such as legal, procurement, occupational safety, allergies, and glove use in surgery, anesthesiology, and other branches of medicine [46, 54, 57, 58]. There were also established commissions providing advice on all latex-related issues.

Creation of a latex safe environment includes implementation of policies aimed at replacing NRL-containing products with synthetic alternatives lacking the compounds, or at identifying such products that emit fewer latex allergens. Switch to powder-free latex gloves helps minimize exposure to natural latex allergens in medical settings and other industries where NRL products are often used [59].

Medical/surgical gloves

From 1980 to 2010, powdered examination/surgical gloves were the primary cause of NRL exposure in clinics and hospitals [48, 59, 60]. The amount of allergenic protein released from latex gloves is a measurable indicator, and some institutions

have switched to synthetic alternatives of products with high NRL content [61–63], while others have completely refused gloves containing hevea [49, 54, 56, 58]. Some healthcare establishments created a safer environment by opting for powder-free latex gloves with low allergen content [64, 65].

It may be time to more broadly reconsider the use of NRL gloves that secrete small amounts of latex or no latex at all, along with synthetic medical gloves, which was especially relevant during the COVID-19 pandemic, when they were in high demand. However, currently, there is no generally accepted value that would enable this process, such as < 0.15 mcg of total Hev b 1, 3, 5 and 6.02 per 1 g of a glove, which would be adopted by manufacturers or regulatory authorities and allow describing the respective items as having low allergenic potential, although this issue is being considered [46]. Moreover, is it possible to control the content of total Hev b at every stage of glove production and ensure it never exceeds < 0.15 mcg per 1 g of a glove [66–68]?

Healthcare workers at high risk of latex allergy and sensitized patients

Institutions employing people with latex allergies must follow strict rules to prevent their exposure to the respective allergens. At a minimum, these rules should allow all workers to use powder-free, low protein latex products, and guarantee sensitized people come in contact with latex-free items only. If colleagues of allergic workers use powder-free latex gloves with low protein content, it can alleviate symptoms in them, but not eliminate them completely [69].

Monitoring of NRL products and the environment

Measuring the amount of hevea allergens released from various products, especially medical gloves, and monitoring the levels of these allergens in the workplace air are crucial to confirmation of the properties of new low protein NRL medical gloves in the context of creation of a safe work environment.

ASTM International has approved three standardized tests designed to assess the safety of NRL-containing products and to monitor airborne allergens in workplaces where these products are used. The preferred one is enzyme immunoassay (IEMA; ASTM D7427-08), since it establishes the content of allergens in the product most accurately. At the same time, other tests for hevea allergens, like competitive inhibition [70] based on human anti-latex IgE, are still used in individual laboratories for research purposes, and require large amounts of serum anti-latex IgE [71].

Hev b 1, 3, 5, and 6.02 are the four key allergens monitored in the environment and reflecting the overall level of allergens therein. In food extracts and environmental samples, they can be quantified with the help of IEMA utilizing monoclonal antibodies with two sites (ASTM D7427-08). It is impossible to establish an item's allergenicity by quantifying only Hev b 1 and Hevamine. The results of ELISA of inhibited IgE has shown that a glove can be labeled as having low allergenic potential if the total concentrations of Hev b 1, 2, 5 and 6.02 in it are below 0.15 mcg per 1 g of glove. For a workplace environment, an earlier study suggested a threshold value of 0.5 ng of latex aeroallergens per g/m3 of air. However, this threshold has not been qualified using ASTM D7427-08 IEMA for allergen content [71–77].

Hevea proteins causing antibody reaction can be detected by an enzyme immunoassay of the ASTM D6499 antigen [78, 79]. This method has limitations: it disallows differentiation of latex allergens that induce IgE and antigens that do not induce IgE. Similar to the total protein study, the test for hevea antigen cannot be used to determine if a product or an environment is latex safe, since this label requires an exact assessment of allergen content.

Modified Lowry method was the initial test allowing to measure the total hevea protein content in food extracts or environmental samples (ASTM D5712) [78, 80]. It is one of the colorimetric techniques for determining proteins in a solution, but low analytical sensitivity limit its usefulness in case of allergenic hevea protein. Moreover, this test disallows distinguishing allergenic and non-allergenic hevea proteins. In 2016, ASTM International published information on an immunological method for determination of 4 allergenic hevea proteins, Hev b 1, 3, 5, 6.02. However, this technique allows qualifying the product as containing allergens, but not quantifying the total amount thereof that the product can release.

NRL alternatives

There have been developed synthetic elastomers and hevea-free rubber (Yulex) that are used in production of commercial rubber-like products:

- Synthetic elastomers such as butyl rubber, neoprene (2-chlorobutadiene polymers), and butadiene and acrylonitrile copolymers are commonly used as an alternative to NRL in medical gloves. These materials contain no allergenic proteins and are therefore safer for healthcare professionals and patients with latex allergies. The most common types of non-latex examination gloves are made of nitrile, neoprene, vinyl or synthetic polyisoprene rubber [81].
- In the past, natural rubber from guayula (Parthenium argentatum) was also used as an alternative to NRL [82, 83]. This plant is extremely low in protein, and appears to have no cross-reactivity with NRL allergens either in vitro or in vivo. However, since 2021, the company manufacturing Guayule products has switched from parthenium to low hevea protein latex supplied from Central America, and uses it in production of consumer goods (wetsuits, and, subsequently, medical gloves) [84].

Individual abstention from latex

General approach

Latex can be found in over 40,000 consumer products used in everyday and medical settings, so people allergic to latex should avoid contact with them [84, 85]. In the USA, medical items containing NRL must be labeled thusly.

Duration of contact restriction and possibility of latex allergy reassessment

It is well known that creating a latex safe environment in medical institutions can help alleviate the symptoms caused by latex and hypersensitivity thereto, as reported by staff and patients. However, within 5 years after last contact, latex-specific IgE antibodies can still be detected in the skin and blood of those avoiding exposure to the substance [48, 49, 56, 70, 86–88]. Therefore, the recommendation is to make contact restriction continued.

People with persisting sensitization, running the risk of re-sensitization, can undergo reassessment relying, in the first place, on anti-NRL IgE assays. Therefore, even if subsequent serological tests return negative, it is necessary to take precautions to prevent the effects of latex allergens.

Reassessments are typical before a necessary medical or dental procedure, or during an annual check-up. Anti-latex IgE serology is the only assessment test available in the USA, approved because of the well-documented latex allergosorbent, consistent assay outcomes, and the capacity to give a semi-quantitative result (kUa/L). *In vivo* skin test methods are not available in the USA due to the lack of approved NRL extracts needed therefor. In Europe, patients can choose between serology and puncture skin test, since at least one approved and well-characterized NRL extract is available there. Unfortunately, it is not present in Russia yet.

Additional management issues

Workplace

In the context of monitoring an employee allegedly allergic to NRL, the first step is to confirm the diagnosis using reliable diagnostic methods [46, 57, 64]. In the USA, this is done with the help of several automatic IgE antibodies analyzers approved by the state. In Europe, an alternative thereto is a skin puncture test with an NRL extract. Once latex sensitivity is confirmed, it is necessary to prevent further contact with NRL at the person's workplace.

Although 15 well-described allergenic components of NRL have been thoroughly studied for diagnostic potential, testing for specific IgE antibodies against individual components of the latex allergen does not increase diagnostic sensitivity for latex-induced occupational asthma compared with the detection of IgE antibodies to a natural extract [89]. However, testing for IgE antibodies to latex components can help distinguish different routes of exposure, such as inhalation (Hev b 5/6.02) and mucosal contact (Hev b 1/3).

In Russia, there are two tests available to the patients, a skin allergy test and a blood test. The former involves applying a small amount of latex allergen solution to the person's skin on the forearm or back. Then, the skin is punctured with a needle to let the solution under it. If the person os allergic to latex, there will appear a blister at the site of application of the solution. Therefore, the test is performed by an allergist or a specially trained doctor. The latter, blood test, implies sending a blood sample to a medical laboratory, where it is analyzed (ELISA) with the aim to find allergen-specific IgE to latex (natural rubber). The units of measurement used are IU (international units)/ml.

It is important have documents supporting claims that deterioration of the person's health and disability are the result of latex exposure in the workplace.

Schools

When a student is diagnosed with a confirmed allergy to NRL, systematic treatment thereof begins with the development of an individual health plan and a school-wide prevention plan. It is extremely important to teach the student self-examination skills, especially when there is a risk of anaphylaxis [90].

Following are the measures recommended for prevention of exacerbation and treatment of allergic reactions in people with latex allergies [84, 91]:

- wearing a medical bracelet signaling of a latex allergy;
- prescription of adrenaline for self-administration to patients with a history of systemic reactions to latex;
- use of non-latex gloves;
- announcing the allergy before any medical, dental, gynecological or surgical procedure, as well as requesting a safe environment for people with latex allergies [92].

Immunotherapy

In the context of treatment of IgE-mediated latex allergy, IT is limited by the lack of extracts approved by regulatory authorities, and frequency and severity of adverse reactions thereto.

Conventional subcutaneous immunotherapy (SCIT) utilizing unpurified latex extracts has been tested in several small randomized trials, and shown varying efficacy [93–95]. One study reported alleviation of the symptoms of urticaria and rhinoconjunctivitis, while another showed decreasing respiratory hyperreactivity to latex. However, adverse events, including systemic reactions, often occurred in all studies. In one test, they were frequent both in the introductory and maintenance phases [93].

Sublingual immunotherapy (SLIT) may offer a lower frequency and severity of adverse events than SCIT [96–100], however, the results vary, and, moreover, there were reported cases of anaphylaxis associated therewith [101–104].

Currently, there is ongoing research of the new approaches to IT that seek to reduce the risk of severe adverse reactions while maintaining or increasing efficacy, such approaches employing recombinant allergens, peptides based on the T-cell epitope, and adjuvants that are conjugated or administered with the allergen [84, 105]. These treatments are still experimental.

CONCLUSION

Thus, latex allergy is a set of pathological conditions that combine intolerance to products made of natural or (less often) synthetic rubber with local or systemic reactions that can significantly affect quality of life. This allergy is caused by sensitivity to proteins contained in NRL, and its manifestations vary from skin irritations to anaphylaxis.

It is important to remember that latex allergy can be prevented. People at risk should carefully choose medical and everyday products, and avoid contact with NRL. Many alternatives (synthetic latex or polyurethane products) can be a safe substitute.

Moreover, educating and raising awareness of this problem are key aspects of the latex allergy management. Despite the challenges posed by the condition, preventive measures and proper management of the situation allow most people with this diagnosis to continue living a full and healthy life. Further research and development of new technologies will also contribute to improving the lives of such people.

References

1. Jacob JL, d'Auzac J, Prevôt JC. The composition of natural latex from Hevea brasiliensis. Clin Rev Allergy. 1993; 11: 325.
2. Alenius H, Kurup V, Kelly K, et al. Latex allergy: frequent occurrence of IgE antibodies to a cluster of 11 latex proteins in patients with spina bifida and histories of anaphylaxis. J Lab Clin Med. 1994; 123: 712.
3. Breiteneder H, Scheiner O. Molecular and immunological characteristics of latex allergens. Int Arch Allergy Immunol. 1998; 116: 83.
4. Smith AM, Amin HS, Biagini RE, et al. Percutaneous reactivity to natural rubber latex proteins persists in health-care workers following avoidance of natural rubber latex. Clin Exp Allergy. 2007; 37: 1349.

5. Palosuo T, Alenius H, Turjanmaa K. Quantitation of latex allergens. Methods 2002; 27: 52.
6. Nowakowska-Swirta E, Wiszniewska M, Walusiak-Skorupa J. Allergen-specific IgE to recombinant latex allergens in occupational allergy diagnostics. J Occup Health. 2019; 61: 378.
7. Sicherer SH. Clinical implications of cross-reactive food allergens. J Allergy Clin Immunol. 2001; 108: 881.
8. Blanco C, Diaz-Perales A, Collada C, et al. Class I chitinases as potential panallergens involved in the latex-fruit syndrome. J Allergy Clin Immunol. 1999; 103: 507.
9. Wright HT, Brooks DM, Wright CS. Evolution of the multi-domain protein wheat germ agglutinin. J Mol Evol. 1985; 21: 28091.
10. Chen Z, Posch A, Cremer R, et al. Identification of hevein (Hev b 6.02) in Hevea latex as a major cross-reacting allergen with avocado fruit in patients with latex allergy. J Allergy Clin Immunol. 1998; 102: 476.
11. Archer BL, Barnard D, Cockbain EG, et al. Structure, composition and biochemistry of Hevea latex. In: Bateman L, editor. The chemistry and physics of rubber-like substances. New York: John Wiley & Sons, 1963; p. 41.
12. Vandenplas O, Larbanois A, Vanassche F, et al. Latex-induced occupational asthma: time trend in incidence and relationship with hospital glove policies. Allergy. 2009; 64: 415.
13. Kelly KJ, Sussman G. Latex Allergy: Where Are We Now and How Did We Get There? J Allergy Clin Immunol Pract. 2017; 5: 1212.
14. Hamann CP, Kick SA. Allergies associated with medical gloves. Manufacturing issues. Dermatol Clin. 1994; 12: 547.
15. Truscott W, Roley L. Glove-associated reactions: addressing an increasing concern. Dermatol Nurs. 1995; 7: 283.
16. Mari A, Scala E, D'Ambrosio C, et al. Latex allergy within a cohort of not-at-risk subjects with respiratory symptoms: prevalence of latex sensitization and assessment of diagnostic tools. Int Arch Allergy Immunol. 2007; 143: 135.
17. Turjanmaa K. Incidence of immediate allergy to latex gloves in hospital personnel. Contact Dermatitis. 1987; 17: 270.
18. Kostyal D, Horton K, Beezhold D, et al. Latex as a significant source of Hevea brasiliensis allergen exposure. Ann Allergy Asthma Immunol. 2009; 103: 354.
19. Liu QL, He XZ, Liang K, et al. Prevalence and risk factors for latex glove allergy among female clinical nurses: a multicenter questionnaire study in China. Int J Occup Environ Health. 2013; 19: 29.
20. Parisi CA, Petriz NA, Busaniche JN, et al. Prevalence of latex allergy in a population of patients diagnosed with myelomeningocele. Arch Argent Pediatr. 2016; 114: 30.
21. Brown RH, Hamilton RG, Mintz M, et al. Genetic predisposition to latex allergy: role of interleukin 13 and interleukin 18. Anesthesiology. 2005; 102: 496.
22. Monitto CL, Hamilton RG, Levey E, et al. Genetic predisposition to natural rubber latex allergy differs between health care workers and high-risk patients. Anesth Analg. 2010; 110: 1310.
23. Charous BL, Tarlo SM, Charous MA, Kelly K. Natural rubber latex allergy in the occupational setting. Methods. 2002; 27: 15.
24. Heese A, van Hintzenstern J, Peters KP, et al. Allergic and irritant reactions to rubber gloves in medical health services. Spectrum, diagnostic approach, and therapy. J Am Acad Dermatol. 1991; 25: 831.
25. Sussman G, Gold M. Guidelines for the management of latex allergies and safe latex use in health care facilities. Am College of Allergy Asthma and Immunology, 1996; p. 56.
26. Williams JD, Lee AY, Matheson MC, et al. Occupational contact urticaria: Australian data. Br J Dermatol. 2008; 159: 125.
27. Kimata H. Latex allergy in infants younger than 1 year. Clin Exp Allergy. 2004; 34: 1910.
28. Cogen FC, Beezhold DH. Hair glue anaphylaxis: a hidden latex allergy. Ann Allergy Asthma Immunol. 2002; 88: 61.
29. Hamilton RG. Diagnosis of natural rubber latex allergy. Methods. 2002; 27: 22.
30. Hamilton RG, Scheer DI, Gruchalla R, et al. Casein-related anaphylaxis after use of an Everlast kickboxing glove. J Allergy Clin Immunol. 2015; 135: 269.
31. Hamilton RG, Adkinson NF Jr. Natural rubber latex skin testing reagents: safety and diagnostic accuracy of nonammoniated latex, ammoniated latex, and latex rubber glove extracts. J Allergy Clin Immunol. 1996; 98: 872.
32. Hamilton RG, Biagini RE, Krieg EF. Diagnostic performance of Food and Drug Administration-cleared serologic assays for natural rubber latex-specific IgE antibody. The Multi-Center Latex Skin Testing Study Task Force. J Allergy Clin Immunol. 1999; 103: 925.
33. Bernardini R, Pucci N, Azzari C, et al. Sensitivity and specificity of different skin prick tests with latex extracts in pediatric patients with suspected natural rubber latex allergy — a cohort study. Pediatr Allergy Immunol. 2008; 19: 315.
34. Hamilton RG, Adkinson NF Jr. Validation of the latex glove provocation procedure in latex-allergic subjects. Ann Allergy Asthma Immunol. 1997; 79: 266.
35. Kelly KJ, Kurup V, Zacharisen M, et al. Skin and serologic testing in the diagnosis of latex allergy. J Allergy Clin Immunol. 1993; 91: 1140.
36. Biagini RE, Krieg EF, Pinkerton LE, Hamilton RG. Receiver operating characteristics analyses of Food and Drug Administration-cleared serological assays for natural rubber latex-specific immunoglobulin E antibody. Clin Diagn Lab Immunol. 2001; 8: 1145.
37. Hamilton RG, Biagini R, Mackenzie B, et al. FDA cleared immunoassays for latex- specific IGE are missing allergenic epitopes from multiple Hev b allergens. J Allergy Clin Immunol. 2002; 109: S259.
38. Seyfarth F, Schliemann S, Wiegand C, et al. Diagnostic value of the ISAC (®) allergy chip in detecting latex sensitizations. Int Arch Occup Environ Health. 2014; 87: 775.
39. Ott H, Schröder C, Raulf-Heimsoth M, et al. Microarrays of recombinant Hevea brasiliensis proteins: a novel tool for the component-resolved diagnosis of natural rubber latex allergy. J Investig Allergol Clin Immunol. 2010; 20: 129.
40. Schuler S, Ferrari G, Schmid-Grendelmeier P, Harr T. Microarray-based component- resolved diagnosis of latex allergy: isolated IgE-mediated sensitization to latexprofilin Hev b8 may act as confounder. Clin Transl Allergy. 2013; 3: 11.
41. Kurtz KM, Hamilton RG, Adkinson NF Jr. Role and application of provocation in the diagnosis of occupational latex allergy. Ann Allergy Asthma Immunol. 1999; 83: 634.
42. Laoprasert N, Swanson MC, Jones RT, et al. Inhalation challenge testing of latex- sensitive health care workers and the effectiveness of laminar flow HEPA-filtered helmets in reducing rhinoconjunctival and asthmatic reactions. J Allergy Clin Immunol. 1998; 102: 998.
43. Kurtz KM, Hamilton RG, Schaefer JA, et al. Repeated latex aeroallergen challenges employing a hooded exposure chamber: safety and reproducibility. Allergy. 2001; 56: 857.
44. Bernardini R, Pucci N, Rossi ME, et al. Allergen specific nasal challenge to latex in children with latex allergy: clinical and immunological evaluation. Int J Immunopathol Pharmacol. 2008; 21: 333.
45. Unsel M, Mete N, Ardeniz O, et al. The importance of nasal provocation test in the diagnosis of natural rubber latex allergy. Allergy. 2009; 64: 862.
46. Bernstein DI. Management of natural rubber latex allergy. J Allergy Clin Immunol. 2002; 110: S111.
47. Sutherland MF, Suphioglu C, Rolland JM, O'Hehir RE. Latex allergy: towards immunotherapy for health care workers. Clin Exp Allergy. 2002; 32: 667.
48. Kelly KJ, Wang ML, Klancnik M, Petsonk EL. Prevention of IgE Sensitization to Latex in Health Care Workers After Reduction of Antigen Exposures. J Occup Environ Med. 2011; 53: 934.
49. Blumchen K, Bayer P, Buck D, et al. Effects of latex avoidance on latex sensitization, atopy and allergic diseases in patients with spina bifida. Allergy. 2010; 65: 1585.
50. Rolland JM, O'Hehir RE. Latex allergy: a model for therapy. Clin Exp Allergy. 2008; 38: 898.
51. Nucera E, Schiavino D, Sabato V, et al. Sublingual immunotherapy for latex allergy: tolerability and safety profile of rush build-up phase. Curr Med Res Opin. 2008; 24: 1147.
52. Chang TW, Wu PC, Hsu CL, Hung AF. Anti-IgE antibodies for the treatment of IgE- mediated allergic diseases. Adv Immunol. 2007; 93: 63.
53. Leynadier F, Doudou O, Gaouar H, et al. Effect of omalizumab in

health care workers with occupational latex allergy. J Allergy Clin Immunol. 2004; 113: 360.
54. Cusick C. A latex-safe environment is in everyone's best interest. Mater Manag Health Care. 2007; 16: 24.
55. SGNA Practice Committee. Guideline for preventing sensitivity and allergic reactions to natural rubber latex in the workplace. Gastroenterol Nurs. 2008; 31: 239.
56. Kelly KJ, Sussman G. Latex Allergy: Where Are We Now and How Did We Get There? J Allergy Clin Immunol Pract 2017; 5: 1212.
57. Bernstein DI, Karnani R, Biagini RE, et al. Clinical and occupational outcomes in health care workers with natural rubber latex allergy. Ann Allergy Asthma Immunol. 2003; 90: 209.
58. Cremer R, Kleine-Diepenbruck U, Hering F, Holschneider AM. Reduction of latex sensitisation in spina bifida patients by a primary prophylaxis programme (five years experience). Eur J Pediatr Surg. 2002; 12 (1): S19.
59. Yunginger JW, Jones RT, Fransway AF, et al. Extractable latex allergens and proteins in disposable medical gloves and other rubber products. J Allergy Clin Immunol. 1994; 93: 836.
60. Kujala V, Alenius H, Palosuo T, et al. Extractable latex allergens in airborne glove powder and in cut glove pieces. Clin Exp Allergy. 2002; 32: 1077.
61. Truscott W. Glove powder reduction and alternative approaches. Methods. 2002; 27: 69.
62. Koh D, Ng V, Leow YH, Goh CL. A study of natural rubber latex allergens in gloves used by healthcare workers in Singapore. Br J Dermatol. 2005; 153: 954.
63. Palosuo T, Antoniadou I, Gottrup F, Phillips P. Latex medical gloves: time for a reappraisal. Int Arch Allergy Immunol. 2011; 156: 234.
64. Brown RH, Hamilton RG, McAllister MA, Johns Hopkins. Latex Task Force. How health care organizations can establish and conduct a program for a latex-safe environment. Jt Comm J Qual Saf. 2003; 29: 113.
65. Stinkens R, Verbeke N, Van de Velde M, et al. Safety of a powder-free latex allergy protocol in the operating theatre: A prospective, observational cohort study. Eur J Anaesthesiol. 2019; 36: 312.
66. Palosuo T, Reinikka-Railo H, Kautiainen H, et al. Latex allergy: the sum quantity of four major allergens shows the allergenic potential of medical gloves. Allergy. 2007; 62: 781.
67. Primeau MN, Adkinson NF Jr, Hamilton RG. Natural rubber pharmaceutical vial closures release latex allergens that produce skin reactions. J Allergy Clin Immunol. 2001; 107: 958.
68. Hamilton RG, Brown RH, Veltri MA, et al. Administering pharmaceuticals to latex- allergic patients from vials containing natural rubber latex closures. Am J Health Syst Pharm. 2005; 62: 1822.
69. Nienhaus A, Kromark K, Raulf-Heimsoth M, et al. Outcome of occupational latex allergy — work ability and quality of life. PLoS One. 2008; 3: e3459.
70. Smith AM, Amin HS, Biagini RE, et al. Percutaneous reactivity to natural rubber latex proteins persists in health-care workers following avoidance of natural rubber latex. Clin Exp Allergy. 2007; 37: 1349.
71. Palosuo T, Alenius H, Turjanmaa K. Quantitation of latex allergens. Methods. 2002; 27: 52.
72. Vandenplas O, Raulf M. Occupational Latex Allergy: the Current State of Affairs. Curr Allergy Asthma Rep. 2017; 17: 14.
73. Yeang HY, Arif SA, Yusof F, Sunderasan E. Allergenic proteins of natural rubber latex. Methods. 2002; 27: 32.
74. Sussman GL, Beezhold DH, Kurup VP. Allergens and natural rubber proteins. J Allergy Clin Immunol. 2002; 110: S33.
75. ASTM D7427-08. Standard test method for immunological measurement of four princi pal allergenic proteins (Hev b 1, 3, 5, 6.02) in natural rubber and its products derived from latex. American Society for Testing Materials, International, West Conshohocken, P A, 19428.
76. Lee MF, Wang NM, Han JL, et al. Estimating allergenicity of latex gloves using Hev b 1 and hevamine. J Investig Allergol Clin Immunol. 2010; 20: 499.
77. Baur X. I are we closer to developing threshold limit values for allergens in the workplace? Ann Allergy Asthma Immunol. 2003; 90: 11.
78. Beezhold DH, Kostyal DA, Tomazic-Jezic VJ. Measurement of latex proteins and assessment of latex protein exposure. Methods. 2002; 27: 46.
79. ASTM D6499. Standard test method for the immunological measurement of antigenic protein in natural rubber and its products. American Society for Testing Materials, International, West Conshohocken, PA, 19428.
80. ASTM D5712-05E1. Standard test method for analysis of aqueous extractable protein i n natural rubber and its products using the modified Lowry method. American Society for Testing Materials, International, West Conshohocken, PA, 19428.
81. Renaud MY. Composition of synthetic latexes used for manufacturing gloves by dipping processes. Clin Rev Allergy. 1993; 11: 363.
82. Siler DJ, Cornish K, Hamilton RG. Absence of cross-reactivity of IgE antibodies from subjects allergic to Hevea brasiliensis latex with a new source of natural rubber latex from guayule (Parthenium argentatum). J Allergy Clin Immunol. 1996; 98: 895.
83. Carey AB, Cornish K, Schrank P, et al. Cross-reactivity of alternate plant sources of latex in subjects with systemic IgE-mediated sensitivity to Hevea brasiliensis latex. Ann Allergy Asthma Immunol. 1995; 74: 317.
84. Sussman G, Gold M. Guidelines for the management of latex allergies and safe latex use in health care facilities. Am College of Allergy Asthma and Immunology. Available from: www.acaai.org/public/physicians/latex.htm.
85. Kostyal D, Horton K, Beezhold D, et al. Latex as a significant source of Hevea brasiliensis allergen exposure. Ann Allergy Asthma Immunol. 2009; 103: 354.
86. Hamilton RG, Brown RH. Impact of personal avoidance practices on health care workers sensitized to natural rubber latex. J Allergy Clin Immunol. 2000; 105: 839.
87. Bernstein DI, Biagini RE, Karnani R, et al. In vivo sensitization to purified Hevea brasiliensis proteins in health care workers sensitized to natural rubber latex. J Allergy Clin Immunol. 2003; 111: 610.
88. Madan I, Cullinan P, Ahmed SM. Occupational management of type I latex allergy. Occup Med (Lond). 2013; 63: 395.
89. Raulf M, Quirce S, Vandenplas O. Addressing Molecular Diagnosis of Occupational Allergies. Curr Allergy Asthma Rep. 2018; 18: 6.
90. Beierwaltes P, Schoessler S. Latex Safe at School: A Student-Centered Approach. NASN Sch Nurse. 2017; 32: 343.
91. Gentili A, Lima M, Ricci G, et al. Secondary prevention of latex allergy in children: analysis of results. Pediatr Med Chir. 2006; 28: 83.
92. American Latex Allergy Association. Available from: www.latexallergyresources.org.
93. Leynadier F, Herman D, Vervloet D, Andre C. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. J Allergy Clin Immunol. 2000; 106: 585.
94. Turjanmaa K, Palosuo T, Alenius H, et al. Latex allergy diagnosis: in vivo and in vitro standardization of a natural rubber latex extract. Allergy. 1997; 52: 41.
95. Sastre J, Fernández-Nieto M, Rico P, et al. Specific immunotherapy with a standardized latex extract in allergic workers: a double-blind, placebo-controlled study. J Allergy Clin Immunol. 2003; 111: 985.
96. Patriarca G, Nucera E, Pollastrini E, et al. Sublingual desensitization: a new approach to latex allergy problem. Anesth Analg. 2002; 95: 956.
97. Nettis E, Colanardi MC, Soccio AL, et al. Double-blind, placebo-controlled study of sublingual immunotherapy in patients with latex-induced urticaria: a 12-month study. Br J Dermatol. 2007; 156: 674.
98. Bernardini R, Campodonico P, Burastero S, et al. Sublingual immunotherapy with a latex extract in paediatric patients: a double-blind, placebo-controlled study. Curr Med Res Opin. 2006; 22: 1515.
99. Nucera E, Schiavino D, Pollastrini E, et al. Sublingual desensitization in children with congenital malformations and latex allergy. Pediatr Allergy Immunol. 2006; 17: 606.
100. Lasa Luaces EM, Tabar Purroy AI, García Figueroa BE, et al. Component-resolved immunologic modifications, efficacy, and tolerance of latex sublingual immunotherapy in children. Ann Allergy Asthma Immunol. 2012; 108: 367.
101. Cisteró BA, Sastre J, Enrique E, et al. Tolerance and effects on

skin reactivity to latex of sublingual rush immunotherapy with a latex extract. J Investig Allergol Clin Immunol. 2004; 14: 17.
102. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. Allergy. 2006; 61: 1236.
103. Buyukozturk S, Gelincik A, Ozşeker F, et al. Latex sublingual immunotherapy: can its safety be predicted? Ann Allergy Asthma Immunol. 2010; 104: 339.
104. Nettis E, Delle DP, Di LE, et al. Latex immunotherapy: state of the art. Ann Allergy Asthma Immunol. 2012; 109: 160.
105. Rolland JM, Drew AC, O'Hehir RE. Advances in development of hypoallergenic latex immunotherapy. Curr Opin Allergy Clin Immunol. 2005; 5: 544.

Литература

1. Jacob JL, d'Auzac J, Prevôt JC. The composition of natural latex from Hevea brasiliensis. Clin Rev Allergy. 1993; 11: 325.
2. Alenius H, Kurup V, Kelly K, et al. Latex allergy: frequent occurrence of IgE antibodies to a cluster of 11 latex proteins in patients with spina bifida and histories of anaphylaxis. J Lab Clin Med. 1994; 123: 712.
3. Breiteneder H, Scheiner O. Molecular and immunological characteristics of latex allergens. Int Arch Allergy Immunol. 1998; 116: 83.
4. Smith AM, Amin HS, Biagini RE, et al. Percutaneous reactivity to natural rubber latex proteins persists in health-care workers following avoidance of natural rubber latex. Clin Exp Allergy. 2007; 37: 1349.
5. Palosuo T, Alenius H, Turjanmaa K. Quantitation of latex allergens. Methods 2002; 27: 52.
6. Nowakowska-Swirta E, Wiszniewska M, Walusiak-Skorupa J. Allergen-specific IgE to recombinant latex allergens in occupational allergy diagnostics. J Occup Health. 2019; 61: 378.
7. Sicherer SH. Clinical implications of cross-reactive food allergens. J Allergy Clin Immunol. 2001; 108: 881.
8. Blanco C, Diaz-Perales A, Collada C, et al. Class I chitinases as potential panallergens involved in the latex-fruit syndrome. J Allergy Clin Immunol. 1999; 103: 507.
9. Wright HT, Brooks DM, Wright CS. Evolution of the multi-domain protein wheat germ agglutinin. J Mol Evol. 1985; 21: 28091.
10. Chen Z, Posch A, Cremer R, et al. Identification of hevein (Hev b 6.02) in Hevea latex as a major cross-reacting allergen with avocado fruit in patients with latex allergy. J Allergy Clin Immunol. 1998; 102: 476.
11. Archer BL, Barnard D, Cockbain EG, et al. Structure, composition and biochemistry of Hevea latex. In: Bateman L, editor. The chemistry and physics of rubber-like substances. New York: John Wiley & Sons, 1963; p. 41.
12. Vandenplas O, Larbanois A, Vanassche F, et al. Latex-induced occupational asthma: time trend in incidence and relationship with hospital glove policies. Allergy. 2009; 64: 415.
13. Kelly KJ, Sussman G. Latex Allergy: Where Are We Now and How Did We Get There? J Allergy Clin Immunol Pract. 2017; 5: 1212.
14. Hamann CP, Kick SA. Allergies associated with medical gloves. Manufacturing issues. Dermatol Clin. 1994; 12: 547.
15. Truscott W, Roley L. Glove-associated reactions: addressing an increasing concern. Dermatol Nurs. 1995; 7: 283.
16. Mari A, Scala E, D'Ambrosio C, et al. Latex allergy within a cohort of not-at-risk subjects with respiratory symptoms: prevalence of latex sensitization and assessment of diagnostic tools. Int Arch Allergy Immunol. 2007; 143: 135.
17. Turjanmaa K. Incidence of immediate allergy to latex gloves in hospital personnel. Contact Dermatitis. 1987; 17: 270.
18. Kostyal D, Horton K, Beezhold D, et al. Latex as a significant source of Hevea brasiliensis allergen exposure. Ann Allergy Asthma Immunol. 2009; 103: 354.
19. Liu QL, He XZ, Liang K, et al. Prevalence and risk factors for latex glove allergy among female clinical nurses: a multicenter questionnaire study in China. Int J Occup Environ Health. 2013; 19: 29.
20. Parisi CA, Petriz NA, Busaniche JN, et al. Prevalence of latex allergy in a population of patients diagnosed with myelomeningocele. Arch Argent Pediatr. 2016; 114: 30.
21. Brown RH, Hamilton RG, Mintz M, et al. Genetic predisposition to latex allergy: role of interleukin 13 and interleukin 18. Anesthesiology. 2005; 102: 496.
22. Monitto CL, Hamilton RG, Levey E, et al. Genetic predisposition to natural rubber latex allergy differs between health care workers and high-risk patients. Anesth Analg. 2010; 110: 1310.
23. Charous BL, Tarlo SM, Charous MA, Kelly K. Natural rubber latex allergy in the occupational setting. Methods. 2002; 27: 15.
24. Heese A, van Hintzenstern J, Peters KP, et al. Allergic and irritant reactions to rubber gloves in medical health services. Spectrum, diagnostic approach, and therapy. J Am Acad Dermatol. 1991; 25: 831.
25. Sussman G, Gold M. Guidelines for the management of latex allergies and safe latex use in health care facilities. Am College of Allergy Asthma and Immunology, 1996; p. 56.
26. Williams JD, Lee AY, Matheson MC, et al. Occupational contact urticaria: Australian data. Br J Dermatol. 2008; 159: 125.
27. Kimata H. Latex allergy in infants younger than 1 year. Clin Exp Allergy. 2004; 34: 1910.
28. Cogen FC, Beezhold DH. Hair glue anaphylaxis: a hidden latex allergy. Ann Allergy Asthma Immunol. 2002; 88: 61.
29. Hamilton RG. Diagnosis of natural rubber latex allergy. Methods. 2002; 27: 22.
30. Hamilton RG, Scheer DI, Gruchalla R, et al. Casein-related anaphylaxis after use of an Everlast kickboxing glove. J Allergy Clin Immunol. 2015; 135: 269.
31. Hamilton RG, Adkinson NF Jr. Natural rubber latex skin testing reagents: safety and diagnostic accuracy of nonammoniated latex, ammoniated latex, and latex rubber glove extracts. J Allergy Clin Immunol. 1996; 98: 872.
32. Hamilton RG, Biagini RE, Krieg EF. Diagnostic performance of Food and Drug Administration-cleared serologic assays for natural rubber latex-specific IgE antibody. The Multi-Center Latex Skin Testing Study Task Force. J Allergy Clin Immunol. 1999; 103: 925.
33. Bernardini R, Pucci N, Azzari C, et al. Sensitivity and specificity of different skin prick tests with latex extracts in pediatric patients with suspected natural rubber latex allergy — a cohort study. Pediatr Allergy Immunol. 2008; 19: 315.
34. Hamilton RG, Adkinson NF Jr. Validation of the latex glove provocation procedure in latex-allergic subjects. Ann Allergy Asthma Immunol. 1997; 79: 266.
35. Kelly KJ, Kurup V, Zacharisen M, et al. Skin and serologic testing in the diagnosis of latex allergy. J Allergy Clin Immunol. 1993; 91: 1140.
36. Biagini RE, Krieg EF, Pinkerton LE, Hamilton RG. Receiver operating characteristics analyses of Food and Drug Administration-cleared serological assays for natural rubber latex-specific immunoglobulin E antibody. Clin Diagn Lab Immunol. 2001; 8: 1145.
37. Hamilton RG, Biagini R, Mackenzie B, et al. FDA cleared immunoassays for latex- specific IGE are missing allergenic epitopes from multiple Hev b allergens. J Allergy Clin Immunol. 2002; 109: S259.
38. Seyfarth F, Schliemann S, Wiegand C, et al. Diagnostic value of the ISAC (®) allergy chip in detecting latex sensitizations. Int Arch Occup Environ Health. 2014; 87: 775.
39. Ott H, Schröder C, Raulf-Heimsoth M, et al. Microarrays of recombinant Hevea brasiliensis proteins: a novel tool for the component-resolved diagnosis of natural rubber latex allergy. J Investig Allergol Clin Immunol. 2010; 20: 129.
40. Schuler S, Ferrari G, Schmid-Grendelmeier P, Harr T. Microarray-based component- resolved diagnosis of latex allergy: isolated IgE-mediated sensitization to latexprofilin Hev b8 may act as confounder. Clin Transl Allergy. 2013; 3: 11.
41. Kurtz KM, Hamilton RG, Adkinson NF Jr. Role and application of provocation in the diagnosis of occupational latex allergy. Ann

Allergy Asthma Immunol. 1999; 83: 634.
42. Laoprasert N, Swanson MC, Jones RT, et al. Inhalation challenge testing of latex- sensitive health care workers and the effectiveness of laminar flow HEPA-filtered helmets in reducing rhinoconjunctival and asthmatic reactions. J Allergy Clin Immunol. 1998; 102: 998.
43. Kurtz KM, Hamilton RG, Schaefer JA, et al. Repeated latex aeroallergen challenges employing a hooded exposure chamber: safety and reproducibility. Allergy. 2001; 56: 857.
44. Bernardini R, Pucci N, Rossi ME, et al. Allergen specific nasal challenge to latex in children with latex allergy: clinical and immunological evaluation. Int J Immunopathol Pharmacol. 2008; 21: 333.
45. Unsel M, Mete N, Ardeniz O, et al. The importance of nasal provocation test in the diagnosis of natural rubber latex allergy. Allergy. 2009; 64: 862.
46. Bernstein DI. Management of natural rubber latex allergy. J Allergy Clin Immunol. 2002; 110: S111.
47. Sutherland MF, Suphioglu C, Rolland JM, O'Hehir RE. Latex allergy: towards immunotherapy for health care workers. Clin Exp Allergy. 2002; 32: 667.
48. Kelly KJ, Wang ML, Klancnik M, Petsonk EL. Prevention of IgE Sensitization to Latex in Health Care Workers After Reduction of Antigen Exposures. J Occup Environ Med. 2011; 53: 934.
49. Blumchen K, Bayer P, Buck D, et al. Effects of latex avoidance on latex sensitization, atopy and allergic diseases in patients with spina bifida. Allergy. 2010; 65: 1585.
50. Rolland JM, O'Hehir RE. Latex allergy: a model for therapy. Clin Exp Allergy. 2008; 38: 898.
51. Nucera E, Schiavino D, Sabato V, et al. Sublingual immunotherapy for latex allergy: tolerability and safety profile of rush build-up phase. Curr Med Res Opin. 2008; 24: 1147.
52. Chang TW, Wu PC, Hsu CL, Hung AF. Anti-IgE antibodies for the treatment of IgE- mediated allergic diseases. Adv Immunol. 2007; 93: 63.
53. Leynadier F, Doudou O, Gaouar H, et al. Effect of omalizumab in health care workers with occupational latex allergy. J Allergy Clin Immunol. 2004; 113: 360.
54. Cusick C. A latex-safe environment is in everyone's best interest. Mater Manag Health Care. 2007; 16: 24.
55. SGNA Practice Committee. Guideline for preventing sensitivity and allergic reactions to natural rubber latex in the workplace. Gastroenterol Nurs. 2008; 31: 239.
56. Kelly KJ, Sussman G. Latex Allergy: Where Are We Now and How Did We Get There? J Allergy Clin Immunol Pract 2017; 5: 1212.
57. Bernstein DI, Karnani R, Biagini RE, et al. Clinical and occupational outcomes in health care workers with natural rubber latex allergy. Ann Allergy Asthma Immunol. 2003; 90: 209.
58. Cremer R, Kleine-Diepenbruck U, Hering F, Holschneider AM. Reduction of latex sensitisation in spina bifida patients by a primary prophylaxis programme (five years experience). Eur J Pediatr Surg. 2002; 12 (1): S19.
59. Yunginger JW, Jones RT, Fransway AF, et al. Extractable latex allergens and proteins in disposable medical gloves and other rubber products. J Allergy Clin Immunol. 1994; 93: 836.
60. Kujala V, Alenius H, Palosuo T, et al. Extractable latex allergens in airborne glove powder and in cut glove pieces. Clin Exp Allergy. 2002; 32: 1077.
61. Truscott W. Glove powder reduction and alternative approaches. Methods. 2002; 27: 69.
62. Koh D, Ng V, Leow YH, Goh CL. A study of natural rubber latex allergens in gloves used by healthcare workers in Singapore. Br J Dermatol. 2005; 153: 954.
63. Palosuo T, Antoniadou I, Gottrup F, Phillips P. Latex medical gloves: time for a reappraisal. Int Arch Allergy Immunol. 2011; 156: 234.
64. Brown RH, Hamilton RG, McAllister MA, Johns Hopkins. Latex Task Force. How health care organizations can establish and conduct a program for a latex-safe environment. Jt Comm J Qual Saf. 2003; 29: 113.
65. Stinkens R, Verbeke N, Van de Velde M, et al. Safety of a powder-free latex allergy protocol in the operating theatre: A prospective, observational cohort study. Eur J Anaesthesiol. 2019; 36: 312.
66. Palosuo T, Reinikka-Railo H, Kautiainen H, et al. Latex allergy: the sum quantity of four major allergens shows the allergenic potential of medical gloves. Allergy. 2007; 62: 781.
67. Primeau MN, Adkinson NF Jr, Hamilton RG. Natural rubber pharmaceutical vial closures release latex allergens that produce skin reactions. J Allergy Clin Immunol. 2001; 107: 958.
68. Hamilton RG, Brown RH, Veltri MA, et al. Administering pharmaceuticals to latex- allergic patients from vials containing natural rubber latex closures. Am J Health Syst Pharm. 2005; 62: 1822.
69. Nienhaus A, Kromark K, Raulf-Heimsoth M, et al. Outcome of occupational latex allergy — work ability and quality of life. PLoS One. 2008; 3: e3459.
70. Smith AM, Amin HS, Biagini RE, et al. Percutaneous reactivity to natural rubber latex proteins persists in health-care workers following avoidance of natural rubber latex. Clin Exp Allergy. 2007; 37: 1349.
71. Palosuo T, Alenius H, Turjanmaa K. Quantitation of latex allergens. Methods. 2002; 27: 52.
72. Vandenplas O, Raulf M. Occupational Latex Allergy: the Current State of Affairs. Curr Allergy Asthma Rep. 2017; 17: 14.
73. Yeang HY, Arif SA, Yusof F, Sunderasan E. Allergenic proteins of natural rubber latex. Methods. 2002; 27: 32.
74. Sussman GL, Beezhold DH, Kurup VP. Allergens and natural rubber proteins. J Allergy Clin Immunol. 2002; 110: S33.
75. ASTM D7427-08. Standard test method for immunological measurement of four princi pal allergenic proteins (Hev b 1, 3, 5, 6.02) in natural rubber and its products derived from latex. American Society for Testing Materials, International, West Conshohocken, P A, 19428.
76. Lee MF, Wang NM, Han JL, et al. Estimating allergenicity of latex gloves using Hev b 1 and hevamine. J Investig Allergol Clin Immunol. 2010; 20: 499.
77. Baur X. I are we closer to developing threshold limit values for allergens in the workplace? Ann Allergy Asthma Immunol. 2003; 90: 11.
78. Beezhold DH, Kostyal DA, Tomazic-Jezic VJ. Measurement of latex proteins and assessment of latex protein exposure. Methods. 2002; 27: 46.
79. ASTM D6499. Standard test method for the immunological measurement of antigenic protein in natural rubber and its products. American Society for Testing Materials, International, West Conshohocken, PA, 19428.
80. ASTM D5712-05E1. Standard test method for analysis of aqueous extractable protein i n natural rubber and its products using the modified Lowry method. American Society for Testing Materials, International, West Conshohocken, PA, 19428.
81. Renaud MY. Composition of synthetic latexes used for manufacturing gloves by dipping processes. Clin Rev Allergy. 1993; 11: 363.
82. Siler DJ, Cornish K, Hamilton RG. Absence of cross-reactivity of IgE antibodies from subjects allergic to Hevea brasiliensis latex with a new source of natural rubber latex from guayule (Parthenium argentatum). J Allergy Clin Immunol. 1996; 98: 895.
83. Carey AB, Cornish K, Schrank P, et al. Cross-reactivity of alternate plant sources of latex in subjects with systemic IgE-mediated sensitivity to Hevea brasiliensis latex. Ann Allergy Asthma Immunol. 1995; 74: 317.
84. Sussman G, Gold M. Guidelines for the management of latex allergies and safe latex use in health care facilities. Am College of Allergy Asthma and Immunology. Available from: www.acaai.org/public/physicians/latex.htm.
85. Kostyal D, Horton K, Beezhold D, et al. Latex as a significant source of Hevea brasiliensis allergen exposure. Ann Allergy Asthma Immunol. 2009; 103: 354.
86. Hamilton RG, Brown RH. Impact of personal avoidance practices on health care workers sensitized to natural rubber latex. J Allergy Clin Immunol. 2000; 105: 839.
87. Bernstein DI, Biagini RE, Karnani R, et al. In vivo sensitization to purified Hevea brasiliensis proteins in health care workers sensitized to natural rubber latex. J Allergy Clin Immunol. 2003; 111: 610.
88. Madan I, Cullinan P, Ahmed SM. Occupational management of type I latex allergy. Occup Med (Lond). 2013; 63: 395.

89. Raulf M, Quirce S, Vandenplas O. Addressing Molecular Diagnosis of Occupational Allergies. Curr Allergy Asthma Rep. 2018; 18: 6.
90. Beierwaltes P, Schoessler S. Latex Safe at School: A Student-Centered Approach. NASN Sch Nurse. 2017; 32: 343.
91. Gentili A, Lima M, Ricci G, et al. Secondary prevention of latex allergy in children: analysis of results. Pediatr Med Chir. 2006; 28: 83.
92. American Latex Allergy Association. Available from: www.latexallergyresources.org.
93. Leynadier F, Herman D, Vervloet D, Andre C. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. J Allergy Clin Immunol. 2000; 106: 585.
94. Turjanmaa K, Palosuo T, Alenius H, et al. Latex allergy diagnosis: in vivo and in vitro standardization of a natural rubber latex extract. Allergy. 1997; 52: 41.
95. Sastre J, Fernández-Nieto M, Rico P, et al. Specific immunotherapy with a standardized latex extract in allergic workers: a double-blind, placebo-controlled study. J Allergy Clin Immunol. 2003; 111: 985.
96. Patriarca G, Nucera E, Pollastrini E, et al. Sublingual desensitization: a new approach to latex allergy problem. Anesth Analg. 2002; 95: 956.
97. Nettis E, Colanardi MC, Soccio AL, et al. Double-blind, placebo-controlled study of sublingual immunotherapy in patients with latex-induced urticaria: a 12-month study. Br J Dermatol. 2007; 156: 674.
98. Bernardini R, Campodonico P, Burastero S, et al. Sublingual immunotherapy with a latex extract in paediatric patients: a double-blind, placebo-controlled study. Curr Med Res Opin. 2006; 22: 1515.
99. Nucera E, Schiavino D, Pollastrini E, et al. Sublingual desensitization in children with congenital malformations and latex allergy. Pediatr Allergy Immunol. 2006; 17: 606.
100. Lasa Luaces EM, Tabar Purroy AI, García Figueroa BE, et al. Component-resolved immunologic modifications, efficacy, and tolerance of latex sublingual immunotherapy in children. Ann Allergy Asthma Immunol. 2012; 108: 367.
101. Cisteró BA, Sastre J, Enrique E, et al. Tolerance and effects on skin reactivity to latex of sublingual rush immunotherapy with a latex extract. J Investig Allergol Clin Immunol. 2004; 14: 17.
102. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. Allergy. 2006; 61: 1236.
103. Buyukozturk S, Gelincik A, Ozşeker F, et al. Latex sublingual immunotherapy: can its safety be predicted? Ann Allergy Asthma Immunol. 2010; 104: 339.
104. Nettis E, Delle DP, Di LE, et al. Latex immunotherapy: state of the art. Ann Allergy Asthma Immunol. 2012; 109: 160.
105. Rolland JM, Drew AC, O'Hehir RE. Advances in development of hypoallergenic latex immunotherapy. Curr Opin Allergy Clin Immunol. 2005; 5: 544.