Latex Allergy: Position Paper

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Abstract
Correct management of latex allergy is essential to ensure adequate care of patients who are allergic to latex, which is ubiquitous in the health care setting. In this Position Paper, the Latex Committee of the Spanish Society of Allergology and Clinical Immunology provides guidelines for the management of latex allergy.

Key words: Latex allergy. Guidelines.

Resumen
El correcto manejo de la alergia al látex es fundamental para garantizar la buena atención de este colectivo de pacientes, dada la ubicuidad de este alergeno en el medio sanitario. El comité de alergia a látex de la SEAIC con este documento de posición pretende resumir de forma clara las directrices a tener en cuenta en esta patología.

Palabras clave: Alergia a látex. Recomendaciones.

Introduction
Natural rubber is obtained from the Hevea brasiliensis tree. It takes the form of a milky aqueous suspension and is extracted by making cuts in the tree bark. Stabilizers and preservatives are then added to prevent it from coagulating [1,2,3].

Rubber products are obtained using 2 different processes: latex concentration and production of natural dry rubber. After harvesting, the latex is centrifuged to obtain 60% dry rubber. Vulcanization accelerators, antioxidants, and other substances are then added, depending on the final characteristics to be obtained [4]. This latex is used to manufacture the objects most frequently associated with allergic reactions such as gloves, condoms, balloons, and catheters [5,6]. In the case of natural dry rubber, the latex is coagulated by reducing its pH with formic acid and acetic acid to produce rubber in the form of sheets or bales, which then undergo 3 phases: malaxation (with additives), moulding, and vulcanization (a type of polymerization which creates a hard, crystalline structure). In this type of processing, the protein content is lower, and vulcanization denaturalizes the proteins that remain [2]. This type of latex is used to manufacture health care products such as stoppers for tubes, pistons, masks, and cannulas [5,6].

History of Latex Allergy
Type IV hypersensitivity to latex additives is well documented and does not differ from other types of contact dermatitis [7]. The first cases of latex allergy through type I hypersensitivity were described in 1927 in Germany [8] and then in 1979[9]. In Spain, the first case was published in 1986 [10]. In the 1980s, the number of cases reported increased considerably, mainly as a result of the confluence of 3 factors [5,6,11]:

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Latex Allergens

Fourteen allergens have been identified (www.allergen.org). Given its plant origins, latex has panallergens and constitutive allergens. In addition, allergens are generated during the manufacturing process (vulcanization). The different allergens sensitize patients in several risk groups through various routes of exposure. Clinical pictures vary, although there is frequently some degree of overlap [16-19].

The allergens characterized to date are as follows:

- **Hev b 1**, or latex elongation factor [18], is a 14-kDa protein involved in the synthesis of polyisoprene. It is a major allergen in patients with spina bifida (54%-100%) and a secondary allergen in health care workers. As it is not soluble in water, its availability by inhalation is low.

- **Hev b 2** is a secondary 34-kDa allergen belonging to the plant defense proteins group. Depending on the geographical region, 5% to 15% of allergic patients are sensitized. No differences in sensitization have been recorded between patients undergoing multiple operations and health care workers [20].

- **Hev b 3** belongs to the rubber particles group and has a molecular weight of 24-27 kDa. It shares its biological function with Hev b 1 and, like Hev b 1, it is insoluble and the major allergen in patients with spina bifida (77%-100%) [21,22]. These allergens cross-react.

- **Hev b 4** is a protein with a microhelix of 50-57 kDa. Its clinical relevance is as yet undefined, although it sensitizes 39% of health care workers [23].

- **Hev b 5** is an acid 16-kDa structural protein whose biological function is unknown. It is the main allergen in different risk groups and is recognized by 92% of health care workers and 56% of patients with spina bifida [24]. For reasons that remain unclear, its prevalence varies from region to region. Hev b 5 presents multiple isoforms and exists in very small amounts in non–amino acid extracts such as those used in diagnosis. Its addition to ImmunoCAP (Phadia) increased the sensitivity of the technique [25]. Hev b 5 shows homology with the kiwi acid protein [26].

- **Hev b 6**, or prohevein (hevein precursor, Hev b 6.01) is a 20-kDa allergen that belongs to the class I chitinases. It has a defensive function, as it degrades chitin, a component in the cell walls of fungi and the exoskeleton of insects. Processing leads to 2 allergic fragments, the N-terminal or hevein (Hev b 6.02) and the C-terminal (Hev b 6.03), which act independently. Hevein is the more important of the two and is a major allergen whose prevalence is greater in health care professionals than in patients with spina bifida [19]. Its sequence shows >50% identity with chitinases from fruits such as banana, avocado, and chestnut, thus giving rise to the latex-fruit syndrome, which is included in cross-reactivity syndromes [27].

- **Hev b 7** is a 43-kDa protein that is more than 50% homologous with patatin, a storage protein in Solanaceae, thus explaining the cross-reactivity with these plants. Hev b 7 is recognized by 23% to 45% of patients [19,23] and is therefore a relevant—but not major—allergen.

- **Hev b 8** is latex profilin. This secondary 14-kDa allergen belongs to the profilins, a group of panallergens that are widespread in plants and that could be responsible for cross-reactivity with exotic fruits such as kiwi and avocado. Although its role as a sensitizing airborne allergen has been questioned in health care workers, it should be taken into account for the correct interpretation of specific immunoglobulin (Ig) E to latex in pollen-sensitive patients. Cross-reactivity may exist between Hev b 8 and pollen profilins; therefore, specific antibodies against latex may have no clinical relevance [28].

- **Hev b 9** is a 32-kDa enolase that cross-reacts in vitro with enolase from fungi of the genera Cladosporium and Alternaria. Its clinical importance is debatable [29].

- **Hev b 10** is a secondary 26-kDa allergen with a superoxide-dismutase function and homology with enzymes of the same function in Aspergillus. It seems to have no clinical relevance [30].

- **Hev b 11** is a secondary 30-kDa allergen belonging to the class I chitinase group [27]. Cross-reactivity with hevein (Hev b 6.02) is low, and its involvement in cross-reactivity with fruits is unknown.

- **Hev b 12** is a secondary 43-kDa lipid transfer protein and Mediterranean plant panallergen that is included in the defense proteins group. No conclusive data exist regarding its possible cross-reactivity with foods [31].

- **Hev b 13** is a 42-46-kDa secondary allergen, although its prevalence has been reported to be 18%-27% [17]. It mainly affects health care workers and, as such, is a relevant allergen.

- **Hev b 14**, also known as hevamine, is a 30-kDa allergen belonging to the chitinase group. Its clinical relevance remains to be determined [32], although it has been identified as a major allergen in the Taiwanese population [33].

The main characteristics of the allergens in terms of clinical relevance are summarized in Table 1. The commercially available ImmunoCAP test can be used to determine specific IgE against the recombinant antigens Hev b 1, 3, 5, 6.01, 6.02, 8, 9, and 11. Specific IgE to rHev b 1,
None of the methods available provides data on the allergenicity of the proteins detected. The modified Lowry method has become the standard, and the analysis of amino acids is also used for some products. Both approaches are used to compare brands. In addition, both methods are used to detect the total amount of proteins present, but do not rule out the presence of residual latex allergens and do not distinguish other proteins that may have been added to the product [57]. Both have been standardized according to European norm UNE-EN-455-3 [58].

The Lowry method is relatively inexpensive and simple. The limit for detecting and extracting total protein from latex gloves has been established at 10 mg per glove, the equivalent of 2 mg/mL of extract, depending on the weight of the glove (European Committee for Standardization) [58].

Amino acid analysis can be used in latex products other than gloves. As it is more sensitive, it can be used to approximate threshold exposure levels.

Methods of measuring specific allergens have not been validated and are not readily available. It is difficult to adapt them for use in industrial plants producing latex or those manufacturing finished products. The protein content of gloves is very variable and ranges from 0 to >1000 mg/g of glove [59]. Results obtained by measuring the total amount of latex protein with the Lowry method have been found to correlate with the biological activity of the latex extracts from gloves [60-63]. Thus, using this method, allergenicity has been associated with low, moderate, and high protein content values [64]. These criteria may be important in the prevention of sensitization to latex.

Measurement of the Amount of Protein in the Air

The environmental concentration of airborne latex allergens is measured by taking samples of environmental air using air samplers in which the latex allergens can be extracted from the filters [34,36-38,41,46]. The samples obtained can be analyzed quantitatively and qualitatively using immunochemical methods [65-67]. An appropriate filter must be used to obtain the desired results. The most suitable filters are those composed of PTFE (Quan-Tec-Air).

Clinical Syndromes

Clinical manifestations induced by type I hypersensitivity reactions to latex proteins vary greatly [68-70] and depend on the route of exposure, the amount of allergen, and individual factors.

Contact Urticaria

Contact urticaria is the most frequent manifestation and may be the only manifestation or that preceding systemic manifestations. Eczema and xeroderma following glove use are nonspecific symptoms [70]. Urticaria is more highly correlated with sensitization to latex than isolated pruritus [71-73]. Contact with the mucosa induces angioedema.

Table 1. Clinical Relevance of Latex Allergens

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hev b 1 and 3</td>
<td>Main allergen in spina bifida</td>
</tr>
<tr>
<td>Hev b 2, 4, 7, and 13</td>
<td>Secondary but relevant allergen in health care workers</td>
</tr>
<tr>
<td>Hev b 6.02 and 7</td>
<td>Verified cross-reactivity with fruits</td>
</tr>
<tr>
<td>Hev b 8, 11, and 12</td>
<td>Panallergens with unknown cross-reactivity with fruits</td>
</tr>
</tbody>
</table>

rHev b 3, rHev b 5, rHev b 6.01, and rHev b 8 is determined using the The hypersensitivity profile of each patient also has therapeutic implications, as the only commercially available vaccine against latex contains the allergens Hev b 5 and 6.

Measurement of Environmental Exposure

Studies quantifying environmental concentrations of airborne latex allergens have been carried out in different health care and hospital environments, ambulances, dental clinics, industrial latex processing plants, as well as on objects used in health care and daily life and in samples of air from urban areas [34,35-50]. The environmental concentrations of the airborne allergens of latex capable of sensitizing and producing symptoms are not well defined, given the complex mixture of potent allergens with differing stability and bioavailability that make up latex, their widespread presence [34], and the lack of sufficiently solid studies [35,51-53]. Increased frequency of sensitization has been associated with concentrations greater than 0.6 ng/m³ in the air of hospital rooms [47]. A concentration of 10 ng/m³ has been proposed as the threshold level for health care environments [37].

Latex allergens are proteins that adsorb to the dust particles present on latex objects. They are aerosolized and behave as airborne allergens of different particle sizes, although most (80%) have a mean diameter >7 μm and a high molecular mass. As the 2 main routes of exposure to latex are the respiratory mucosa and the skin, both environmental air and surfaces should be monitored [53]. Latex allergens may be present as individual particles or may adhere to the surface of other particles [54-63].

Measurement of the Amount of Protein in Latex Objects

Samples from surfaces may be collected using 3 techniques:
1. By simply collecting the sample with tweezers and storing it in a sterile container or bag
2. By passing a polytetrafluoroethylene (PTFE) filter over the surface in question in order to trap the allergens
3. By aspirating the surface
No suitable method exists for measuring latex allergens in manufactured products; therefore, the amount of latex protein that can be extracted should be determined.
Latex is the most common cause of occupational contact urticaria [74]. Dermatitis of the hands caused by irritants may foster sensitization to latex. Urticarial lesions that are mediated by type I hypersensitivity to latex proteins and become chronic could result in protein contact dermatitis [74]. Clinically, protein contact dermatitis manifests as chronic eczema with episodes of recurrent acute attacks. It represents a combination of immediate-type hypersensitivity (type I) and delayed-type hypersensitivity (type IV).

**Allergic Rhinitis and Asthma**

Allergic rhinitis and asthma mainly affect individuals exposed via inhalation, such as health care professionals and workers who use protective gloves or who are exposed to latex in their work environment [40,70,75-84]. Powdered gloves are the main source of reactions to environmental latex [10,69,75,85-88].

Latex is considered to be an occupational allergen [34,88-94] and is the cause of occupational asthma in the professions affected, with a prevalence of between 2.5% and 10% [94-98]. Eosinophilic bronchitis due to latex is an infrequent occupational respiratory manifestation [99].

**Systemic Reactions**

Latex is the second cause of intraoperative anaphylaxis after muscle relaxants [100,101]. The frequency of perioperative anaphylaxis attributed to latex has remained relatively stable in recent years, with a slight increase according to recent data: a minimum of 12.1% was reached in 1997-1998 and a maximum of 22.3% in 2001-2002 [102].

Cardiovascular collapse is the most common form of presentation in anesthetized patients, although skin rash and bronchospasm are also frequent [100-103].

Reactions to latex normally occur during the maintenance phase of anesthesia, unlike anaphylaxis due to muscle relaxants and opiates, which is more frequent in the induction phase. Abdominal, gynecological, and orthopedic operations present the greatest risk [104-108], although barium contrast enema and anorectal manometry should also be borne in mind [109-111].

In children, latex is involved in 27% of anaphylactic reactions following anesthesia, with higher figures in those aged under 5 years [105]. The population at risk of suffering an anaphylactic reaction to latex after an operation or medical examination can be divided into individuals with a genetic predisposition (atopic) or individuals with higher levels of exposure (health care workers and patients undergoing multiple operations or tests) [106].

Latex proteins from gloves can be transferred to food handled using gloves. These proteins can cause anaphylactic reactions in sensitized individuals who subsequently consume the food [111-113]. To avoid latex acting as a hidden allergen in such cases, the Spanish Agency of Food Safety and Nutrition (Agencia Española de Seguridad Alimentaria y Nutrición) has issued a recommendation to avoid the use of latex gloves in food companies [114].

**Latex-Fruit Syndrome**

Latex-fruit syndrome involves cross-reactivity between inhaled and food allergens [115-121]. Anaphylaxis to both latex and foods is common [115,122-125] and may be the initial manifestation.

The clinical features of latex-fruit syndrome have been described by different authors in different countries [126-131] and can be summarized as follows:

(a) The association between latex allergy and fruit allergy ranges between 21% [120-130] and 58% [116,126]. This variability can be explained by the differences in diagnostic criteria and eating habits [118,126]. The frequency of sensitization to foods without symptoms is very high [128].

(b) The foods most frequently involved are chestnut, avocado, banana, and kiwi, although many others are involved [118,119,127,128].

(c) The spectrum of clinical reactions to foods is very wide. The proportion of anaphylactic reactions caused by foods ranges from 50% [115] to less than 5% [119]. Banana, avocado, chestnut, and kiwi are associated with anaphylaxis [115,118]. Other foods (eg, fig, papaya, and tomato) are more frequently associated with latex allergy, although they can also cause anaphylactic reactions. In contrast, foods such as potatoes can occasionally cause mild local reactions [118].

Although latex allergy precedes hypersensitivity to foods in most patients, the reverse may also occur. Several studies have shown that, in many cases, the spectrum of food allergies may increase over time [115,120].

Among the main latex allergens, class I chitinases, which have a hevein N-terminal domain, have been considered responsible for latex-fruit allergy syndrome [42], although other plant panallergens that are present in latex, such as glucanase (Hev b 2), profilin (Hev b 8), LTP (Hev b 12), or even isolated hevein domains, may play an important role [129,130].

**Clinical Manifestations in Spina Bifida**

The prevalence of latex allergy is greater in children with spina bifida than in the general population [131,132]. The fundamental risk factor is the number of operations [133-135]. Other factors, such as elevated IgE titers, presence of a ventriculoperitoneal shunt during the first days of life, and atopy also increase the risk [136-139].

Exposure to latex in these children is via several routes (mucosa, blood vessels, and inhalation).

The most frequent manifestation is urticaria-anгиоedema, in contrast with healthy care workers, who exhibit respiratory symptoms. The most relevant allergen appears to be Hev b 1 [140].

**Diagnosis of Latex Allergy** (Figure 1)

Diagnosis of latex allergy is based on clinical suspicion, although this is not always easy to establish [7,141,142]. The sensitivity and specificity of a good clinical history taken by an experienced allergologist are very high [143]. The history should record the presence or absence of other allergies, atopy,
Previous operations or medical procedures involving latex products, and whether the patient belongs to an identified risk group [144,145]. Exhaustive questions should be asked regarding the possible source of exposure [146], and note should be taken of the existence of any acute episodes of anaphylaxis or urticaria with no known cause. Finally, patients should be questioned about reactions induced by contact with or ingestion of fruits, particularly kiwi, chestnut, avocado, and banana [115].

Specific questionnaires may be useful, thanks to their high sensitivity, although they lack specificity. They are especially useful in the identification of sensitized and asymptomatic patients belonging to high-risk groups [144] and in studies of prevalence [147].

The complementary diagnosis is based on skin tests and the determination of specific IgE using the different methods available. A positive result in any of these may be considered indicative of sensitization to latex [148], that is, the presence of specific IgE antibodies, although, as these can be detected in asymptomatic individuals, the results should not be analyzed without the clinical history.

**Skin Tests**

**Prick tests**

Prick tests are considered the method of choice to confirm or rule out latex allergy [150]. Standardized extracts can provide a sensitivity of 93% with a specificity of 100% [151-153] and are considered safe, although isolated cases of anaphylaxis have been reported [154]. Intradermal tests are not recommended.

**Patch tests**

Patch tests are used in suspected delayed-type hypersensitivity reactions, most of which are not attributable to latex but to additives. With the exception of mercaptobenzothiazole and N,N-para-phenylenedianine, it is advisable to test mixtures of substances (carba mix, paraphenylenedianine mix, and thiuram mix) instead of each additive separately [154-158]. Latex patches without additives are not recommended [156], although exceptional cases of contact dermatitis due to latex itself have been reported in negative prick tests [154,157-160].

**Laboratory Tests**

**Determination of specific IgE against latex**

Sensitivity using CAP (Phadia) or AlaSTAT (Diagnostic Products Corporation) is high [161-163]; however, it may vary widely between the different methods available, especially when high-risk populations such as health care workers are analyzed and the clinical history is not taken into account [141,164]. When the clinical history is taken into account and a positive cutoff point is established at >0.35 kU/L, both techniques show similar sensitivity (97% and 100%, respectively) with specificities of 83% for CAP and 33% for AlaSTAT [165,166].

Determination of recombinant allergens using CAP may confirm the diagnosis in cases where sensitization has not been proven by other techniques and is useful for establishing profiles of sensitization to different allergens in different groups of patients [167]. Another means of detecting specific IgE is by ImmunoCAP ISAC (CRD 112) (Phadia), in which the components of purified allergens are fixed on a biochip. In a 2-phase assay, the antibodies from the patient’s serum bind to the components of the fixed allergens. After a brief washing phase, the antibodies bound to the allergens are detected using a fluorescent antibody. The results of this semiquantitative test are expressed in ISAC standardized units. The latex allergens available are rHev b 1, rHev b 3, rHev b 5, rHev b 6.01, and rHev b 8. Immunoblotting can also be used to detect specific IgE, but always as a complement to another diagnostic technique [168].

**Flow cytometry**

Flow cytometry has proven efficient in the diagnosis of latex allergy [169-172], even in children and using recombinant allergens [171], with a sensitivity greater than 93% and a
specificity of 91.7% [172,173]. The technique is not widely used, given its high cost.

**Challenge Tests**

Challenge tests are indicated when the clinical history is suggestive and complementary diagnostic tests (skin or laboratory tests) are negative or contradictory [6]. They may also be used to rule out latex allergy in asymptomatic sensitized patients.

**Rubbing test**

The rubbing test gives false positives and is not standardized. Thus, its diagnostic yield is very low and it is not used [174].

**Glove use test**

Considerable disparity exists between glove use protocols, with exposure times ranging from 15 minutes to 2 hours. In general, the first step involves placing a fingertip of the glove on a dampened finger; if the result is negative, the complete powdered glove is put on. A vinyl or nitrile glove is used on the other hand as a negative control. The result is considered positive if contact causes erythema, pruritus, blisters, or respiratory symptoms.

The main limitations of the glove use test are the difficulty in blinding, thus favoring false positives, and the existence of false negatives, especially in patients who have avoided latex for a long time. The test has been used in different groups of patients, including children with spina bifida [175,176].

**Specific bronchial challenge test**

Bronchial challenge tests have been performed using different methods and are classified into those that use an aqueous latex extract (with a nebulizer or in a chamber with aerosolized glove extract) and those consisting of handling or shaking gloves to generate a dust aerosol [177-183].

Conjunctival challenge [184] and nasal challenge [185] have also been used, although they are generally of little value.

**Diagnosis of Food Allergies Associated With Latex Allergy (Figure 2)**

Skin prick test with the fresh fruit involved in the latex-fruit syndrome shows 80% agreement with the clinical diagnosis and is a simple, inexpensive, and reproducible way to confirm clinical suspicion. If the different fruits are analyzed separately, agreement is lower with papaya and kiwi (around 60%) than with banana, avocado, and chestnut (close to 90%). The commercially available extracts with the fruits involved in the syndrome have a diagnostic sensitivity lower than that of the prick test, probably due to a lack of standardization [128].

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![Figure 2](image-url)
Similarly, the diagnostic sensitivity of specific IgE against fruits using the CAP method is substantially lower than that of the clinical history and the skin prick test with fruit. Determination of specific IgE against avocado (near 80%) is better than against the other fruits involved [119,128].

**Treatment**

The mainstays of management of latex allergy are treatment of the present reaction and prevention of future reactions.

Patients with allergic reactions to latex should receive standard treatment (depending on severity) using latex-free material in a latex-free environment. Patients must be reminded of the importance of carrying an epinephrine self-injector. Neither of the 2 self-injectors commercially available in Spain—Alteless and Jext—contains latex.

However, it is also important to implement adequate measures to avoid future reactions, namely, patient education, avoidance of contact with latex objects, and treatment with specific immunotherapy.

**Patient Education**

Patients must understand the importance of identifying themselves as allergic to latex and knowing where latex may be present and how to avoid it (see 7.2, Avoidance of Latex Objects). This precaution is particularly important in the health care setting. If a patient is admitted to hospital, latex allergy should be stated clearly and unequivocally in the clinical history, the nursing notes, the surgical report (where applicable), and at the head of the patient’s bed. Furthermore, patients should wear a medical bracelet warning of the danger.

**Avoidance of Latex Objects**

Full avoidance of latex is considered impossible, given its widespread use [186,187], although it is frequently not necessary in most allergic patients, who tolerate exposure to everyday rubber objects [62,188].

Table 2. Objects Used in Health Care Settings That May Contain Latex

<table>
<thead>
<tr>
<th>Catheters</th>
<th>Syringes</th>
<th>Stoppers</th>
<th>Elastic bandages</th>
<th>Drains</th>
<th>Respirator tubes</th>
<th>Tourniquets</th>
<th>Nasogastric tubes and catheters</th>
<th>Compression stockings</th>
<th>Masks</th>
<th>Balloons</th>
<th>Handles</th>
<th>Footwear</th>
<th>Ventriculoperitoneal shunt</th>
<th>Stethoscope tubes</th>
</tr>
</thead>
</table>

*The list is not exhaustive.

<table>
<thead>
<tr>
<th>Table 3. Commonly Used Objects Containing Latex*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesives</td>
</tr>
</tbody>
</table>

*The list is not exhaustive.

Avoidance measures are also implemented in patients with suspected latex allergy pending confirmation [189]. The written information given to latex-allergic patients about their illness must include a list of objects that could contain latex (Tables 2 and 3) and details of suitable alternatives, including latex-free gloves and condoms.

For further details, see 8.3 Secondary Prevention.

**Alternatives to latex for the manufacture of gloves and other medical products**

Alternatives to latex exist for most rubber objects and include neoprene, polyvinyl chloride, silicone, polyurethane, and vinyl. In the case of medical devices, alternatives can be found in different publications and on the Internet (www.latexallergylinks.tripod.com, www.latexallergy.ndo.co.uk, www.latexallergyresources.org).

Most important is the substitution of latex gloves, the main source of latex allergens in the health care setting. Not all the alternatives are suitable for all the procedures carried out in hospitals.

Polyvinyl chloride (or simply vinyl) gloves do not have the same barrier effect as latex gloves [190-193] and, as such, are not a valid alternative as protection against infection. Nitrile


Avoidance of foods with cross-reactivity to latex

Patients with latex-fruit syndrome should be advised to avoid the fruits involved. No consensus has been reached on the avoidance of the 4 highest-risk foods, although no previous reactions to these foods have been reported, not even in the presence of subclinical sensitization or specific IgE against the main allergens causing this reactivity.

Specific Immunotherapy

Although considered an alternative, immunotherapy with latex has only been analyzed in 7 published studies using the parenteral or sublingual route [195-203]. All conclude that while the clinical sensitivity of patients can be reduced, the incidence of important adverse reactions is too high to recommend its habitual use, except under very controlled conditions and in very specific cases [203,204].

Prevention

Preventing latex allergy depends on the type of prevention chosen (primary or secondary), the clinical characteristics of the at-risk or sensitized individual, and the possibility of daily avoidance.

Current Regulations Regarding the Presence of Latex in Objects

General regulations

In Spain, health care products are regulated by Royal Decree 414/1996 of March 1, which transfers to the Spanish legal system Directive 93/42/EEC of June 14, 1993 concerning medical devices. Both European Union and Spanish regulations represent the legislation through which the conditions for the manufacture and commercialization of health care products are established.

Labeling

One of the most crucial needs for allergic patients is correct labeling of all latex products in order to facilitate immediate identification and thus enable the individual to avoid contact. In single-use medical gloves, provision of a label reading "Contains latex from natural rubber, which may cause allergic reactions" is regulated in UNE-EN 455-3. For other health care products a directive exists regarding the implications of latex allergy in health care workers [218]. Table 5 summarizes the main published studies on primary prevention programs in health care workers [219-226].

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Table 5. Studies Assessing the Efficacy of Prevention Measures in Health Care Professionals

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Prevention Strategy</th>
<th>Diagnostic Method</th>
<th>Efficacy Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allmers et al (225)</td>
<td>Health care workers in Germany</td>
<td>Unpowdered gloves low in proteins</td>
<td>Questionnaire, skin test (challenges in some)</td>
<td>110 new cases/year (1997) 17 new cases/year (2001)</td>
</tr>
<tr>
<td>Hunt et al (221)</td>
<td>Health care workers (Mayo Clinic) N=12000</td>
<td>Unpowdered gloves low in proteins</td>
<td>Questionnaire, skin test</td>
<td>Allergic patients: Incidence rate of 0.15% before 1993 0.027% after 1993</td>
</tr>
</tbody>
</table>

Abbreviation: Ig, immunoglobulin.

Secondary Prevention

In both sensitized and allergic patients, the most effective approach is avoidance; however, this is difficult, given the widespread presence of latex. Therefore, changes in the use of latex at home, school, and work and in the health care setting should be considered.

Secondary prevention in the health care worker

The use of unpowdered gloves and gloves with a low latex protein content leads to a reduction in the number of patients with symptoms and the concentrations of specific IgE [216,227-230]. Powdered gloves with low allergenicity lead to a significant reduction in hand eczema, thus allowing health care workers to remain in their posts [226,224]. As for reduction in the onset of symptoms, other studies seem to confirm the usefulness of latex avoidance measures, which also enable health care workers to continue to perform their work activities [230-266].

Secondary prevention in patients in the health care setting

Surgical operations are one of the most difficult issues to resolve, especially adequate preparation of operating rooms. Several published protocols (mostly in nursing journals) advise different diagnostic and therapeutic procedures in latex-allergic patients [231-237].

Secondary prevention in patients outside the health care setting

Some authors have pointed out that it is impossible for patients to completely avoid latex in their daily lives, even though this would only be a real problem in a small group of highly sensitized patients prone to very severe reactions [238-241].

The quantity of information available is vast. In Spain, several patient associations, eg, the Spanish Association of Latex-Allergic Patients (Asociación Española de Alérgicos al Látex [http://www.alergialatex.es] and the Spanish Association of Food-Allergic and Latex-Allergic Patients (Asociación Española de Alérgicos a Alimentos y Látex [http://www.aepnaa.org]), provide information in Spanish. Scientific associations such as the Spanish Society of Allergology and Clinical Immunology (http://www.seaiac.es) and the Scientific Society of Allergology and Clinical Immunology for Madrid and Castilla la Mancha (http://www.smclm.com) also provide information on the issue.

Despite the quantity of information available to latex-allergic patients, reactions are still reported sporadically. These are sometimes very severe, as a result of contact with latex as a hidden allergen in foods [72,113,242-244], toys, or other objects [245-247]. Such cases show the inefficiency of secondary prevention measures outside the health care setting [237-240].

Further studies are needed to broaden information on the efficacy of avoidance measures outside the health care setting, as well as their repercussion on quality of life [248].

Unresolved Issues

Despite research efforts, many important aspects of latex allergy have yet to be clarified. For example, greater
understanding of the natural progression of latex allergy in the general population would help to distinguish asymptomatic sensitization from real clinical allergy, interpret the different IgE responses to each of the allergenic latex proteins [249], establish the number of patients with asymptomatic sensitization who would develop symptomatic allergy [250-257,285-90], and decide on the appropriate follow-up for these patients. Increased knowledge would also help us to determine the clinical yield of preventive measures [258] and whether such measures should include avoidance of latex, especially when patients need to undergo medical or surgical procedures. Finally, the more data available, the more likely we are to know the complete range of risk factors for latex allergy [259]. In this context, a better understanding of the genetic polymorphisms associated with latex allergy would enable us to avoid latex exposure in allergic patients [260-264].

Another unresolved issue concerns allergy to plant foods whose allergens cross-react with latex [98,128]. We do not have precise and useful markers that enable us to identify which patients who are initially allergic to latex but not allergic to foods are at greatest risk of experiencing future allergic reactions when they come into contact with the foods in question.

We must also determine whether latex-allergic patients who follow a strict and prolonged avoidance regimen, especially in the workplace, and who achieve undetectable concentrations of specific IgE against latex, could overcome their illness and be considered cured. Similarly, the progression of patients who become allergic following early and continuous exposure to latex, such as those with spina bifida or those undergoing multiple operations, remains to be determined.

More high quality prospective studies are necessary to show whether prevention measures can really reduce the incidence of latex allergy in the workplace and the economic repercussions that this would have as regards sick leave and disabilities [15,73,219,224,258,265].

Specific immunotherapy must be further developed. Production of modified biotechnical allergens with lower allergenicity will likely reduce the number of adverse reactions [266-270].

The controversy surrounding the real risk of exposure to hard objects manufactured from rubber for latex-allergic individuals needs to resolved [271]. Many articles have been published of single cases or small groups of patients who have occasionally experienced reactions following exposure to these hard rubber objects, although such reports do not objectively demonstrate that the reaction was due to latex [272-278].

Finally, ways of identifying new at-risk groups need to be defined [279].

**Key Points**

- It is possible to determine the amount of latex protein both in environmental air and on the surface of objects using immunoanalysis techniques and immunoblotting.
- All patients with suspected latex allergy should be referred to an allergologist for study.
- The clinical history is fundamental for diagnosis and should be completed with skin tests using the prick technique with appropriately validated extracts and occasionally also with the determination of specific IgE (against latex and recombinant allergens) and exposure tests.
- The natural progression of latex allergy in the general population is not well defined. It is best known in children with spina bifida or those undergoing multiple operations, although we are a long way from establishing a “route map for latex allergy”.
- In occupational allergy to latex, sensitization appears to be proportional to the use of powdered latex gloves; consequently, replacement with unpowdered gloves or gloves containing no latex is recommended.
- Avoidance of reactions to latex involves educating patients and health care staff about latex allergy and the main sources of latex, paying special attention to soft rubber objects, and increasing knowledge of which plant foods may present clinical cross-reactivity with latex, especially banana, chestnut, avocado, and kiwi.
- In latex-allergic patients, associated allergy to foods must be ruled out, as must be latex allergy in patients allergic to specific fruits, especially banana, chestnut, avocado, and kiwi.
- All latex-allergic patients must be provided with a written report showing their diagnosis and setting out recommendations. Patients should carry a copy of the report with them at all times.
- Both patients and health care staff must know the different latex materials that can be used in medical and everyday settings that do not pose any risk for patients. Health centers must have action plans for latex-allergic patients.
- Indications for specific immunotherapy are limited. More clinical trials are required to define its clinical usefulness.
- Primary prevention protocols in children with spina bifida reduce the frequency of sensitization to latex; therefore, these children must avoid exposure to latex from birth. It would be advisable to apply this measure universally to other at-risk groups in the pediatric population.
- No published studies evaluate the efficacy of primary prevention programs in workers exposed to latex outside the health care setting.
- The use of unpowdered gloves and those with a low protein content lowers the incidence of latex allergy in health care workers and reduces the severity of symptoms in those who have already become sensitized. Few data are available from outside health care settings.
- Although it is not possible to achieve a completely latex-free health care environment, the use of avoidance protocols and substitution of latex materials will enable latex-allergic patients to safely undergo diagnostic and therapeutic procedures.

• As several aspects of this disease have yet to be clarified, further research should be encouraged.

References


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