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LETTER TO THE EDITOR

Latex allergy: advantages of molecular diagnostics during coronavirus

M. De Amici[1], F. Barocci[2], A. Licari[3,4], S. Caimmi[3], A. Marseglia[3], G. Testa[3], C. Torre[5] and G.L. Marseglia[3,4]

[1]Immuno-Allergology Laboratory of Clinical Chemistry and Pediatric Clinic, Foundation IRCCS Policlinic San Matteo, Pavia, Italy; [2]Medicine Unit Laboratory, ASST Rhodense Garbagnate Milanese, Rho, Italy; [3]Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [4]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; [5]Laboratory of Clinical Chemistry, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

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To the Editor,

Although in 1927 Stern described for the first time the allergic reactions to natural rubber latex (NRL), only in recent decades a significant effort has been made to reduce the incidence of latex allergy. Latex is a whitish milky secretion containing many substances of which about only 2% are proteins. Most are removed when the latex is processed, only a small fraction remains in the finished product which is involved in the onset of allergic reactions. Some commercial firms have carried out intense research to reduce the protein content (through double or triple centrifugation). Latex is present in much of the healthcare equipment used, such as catheters, balloons, nasogastric tubes, gloves, urinary catheters, endotracheal tubes, ventilation tubes. During latex processing chemical antioxidants are added which can also cause type IV hypersensitivity reactions. Since 1979 IgE-mediated allergy to NRL has been recognized as a major health problem, with vast economic implications, especially in patients who are candidates to surgical operations (1). Latex allergy caused by gloves worn or aerosol particle inhalation has also become frequent among healthcare professionals.

The coronavirus disease pandemic 2019 (COVID-19) has led to an increase in the use of latex aids, therefore, in allergic conditions, a correct diagnostic evaluation is advantageous. In fact, in relation to the pandemic, there has been a notable increase in the use of latex gloves in both work and private environments, as it is the material that maintains integrity longer during use, for example, compared to vinyl ones which break more easily and do not mould to the hand. The use of latex gloves helps prevent infections only through correct use - they must be appropriately disposed of and changed every time after use [according to the instructions of the Istituto Superiore di Sanità (ISS)]. The need for Personal Protective Equipment (PPE) can create problems for latex allergic individuals and is also a risk for others who may unintentionally develop a latex allergy from repeated use of this type of glove.

In the 1980s, there was an increased demand for latex gloves to protect healthcare workers resulting in a latex allergy epidemic with various symptoms, from contact dermatitis, itchy, watery eyes and nose, asthma and anaphylaxis. Therefore, it is essential not to forget what was learned in the 1980s and 1990s

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Corresponding Author:
Dr Fiorella Barocci,
Medicine Unit Laboratory,
ASST Rhodense - Garbagnate Milanese,
Rho (Milan), Italy
Tel.: +39 3385065564
e-mail: fiorellabarocci@yahoo.it

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regarding the potential development of latex allergy and prevent exposure to already allergic individuals.

According to the publications in "The Journal of The European Academy of Dermatology and Venereology" the dermatologists of Lecco Hospital found that a large number of patients hospitalized with ongoing COVID-19 infection, but also asymptomatic ones, who had skin lesions of the extremities (hands, feet): red spots, swelling and itching/burning sensation. Therefore, it is essential to distinguish COVID-19-related cutaneous manifestations from other closely resembling skin lesions, including -allergic skin reactions to latex.

Latex allergy may outbreak as an immuno-mediated mechanism associated with clinical symptoms, including immediate reactions via immunoglobulins and/or the delayed reactions mediated by lymphocytes. These are also known as allergic contact dermatitis and are caused by sensitization to rubber products induced by additives such as thiurams, carbamates, mercaptans, diphenyl guanidine, and antioxidants, which prevent deterioration of the rubber. The IgE-mediated allergy is caused by direct contact of the products in latex with the skin or by inhalation of airborne latex particles. The protein part of the latex stimulates the production of specific IgE (sIgE) with their corresponding antibody response and it is possible to relate awareness of latex reaction to the development of symptoms such as rhinitis, conjunctivitis and/or allergic asthma (1), however, in addition, anaphylactic reactions are also possible (2). The allergenic sources for the population at risk are surgical and domestic gloves, catheters, condoms,

Table I. *The two main allergens of latex*

Major Allergen	**Characteristics**
Hev b 1 (14,6KdA)	An insoluble allergenic latex specific protein insoluble in water and located on the surface of the rubber particles of larger size
Hev b 3 (24kDa)	An insoluble allergenic protein located on the surface of the rubber particles of smaller dimensions. HEV b 1 and HEV B 3 are strongly associated with latex allergy in subjects exposed to repeated surgical operations

Table II. *Major allergens of latex with important cross-reactive properties towards foods*

Major Allergen	**Characteristics**
Hev b 5 (16 kDa)	A powerful heat stable allergenic. The protein is homologous to protein fractions identified in kiwi and potato. The IgE positivity specifications are prevalent in HCW patients
Hev b 6.02 (5 kDa)	A small allergenic protein (hevein) cross-reacting with avocado, chestnut, banana, kiwi. Despite the considerable cross-reactivity between these allergens, no correlation was found between latex-fruit syndrome and hevein sensitization or hevein-like domains. Specific IgE are significantly prevailing in HCW.

accessories for the cleaning of washable rubber, hemostatic laces, pacifiers for children and balloons and toys. These are just some examples of articles that may contain latex proteins capable of causing IgE-mediated allergy.

Hepner and Castells published an extensive list of latex-containing products used in operating theaters, in post-anesthesia, in the care unit, in addition to those presently available in the community, together with alternative latex-free products. The exposure to natural rubber latex may be either direct by skin or mucous membrane contact, or by inhalation. Children with spina bifida (SB), health care workers (HCWs), subjects with a history of several surgical procedures, non-HCWs with exposure to latex such as chemical and pharmaceutical products, food chain workers, cleaners, workers in greenhouses, hairdressers, workers in the food industry and 'rubber industry', and subjects with food allergy and atopy, belong to a group with a high risk of developing an allergy to NRL3. To date, characterized and standardized allergenic extracts have been used to determine specific IgE; however, molecular biology has finally provided more accurate tools and bypassed the problem of standardization of the complex and heterogeneous extracted NRL.

The most common worldwide serum testing detects bound IgE using an enzymatic reagent in an *in-vitro* assay. Serological diagnostics has evolved with the identification and use of the individual antigenic components. The use of recombinant allergens allows to identify the allergenic profile of each patient which allows the clinician to make accurate assessments. The individual molecular components must be used when the latex (k82) has a concentration >1KUA/l. Without specialist request, it is preferred, on the advice of clinical allergologists, to have cut-off > 1 KUA/l "recommended" to execute recombinants. Otherwise a cut-off > 0.1 KUA/l remains valid (3). Therefore, the Component Resolved Diagnosis (CRD) provides for the use of the following molecular components in allergological diagnostics *in vitro*: (k215) Hev b 1, (k217) Hev b 3, (k218) Hev b 5, (k219) Hev b 6.01 , (k220) Hev b 6.02, (k222) Hev b 9, (k224) Hev b 11 e (k221) Hev b 8 (profilin). One or more profiles may be created according to the characteristics of the sample (child, HCW, preoperative) or provide text reflex without distinction of the origin.

Recently 15 different allergenic latex components have been well characterized for their biological function, physiological role and, above all, for their allergenic potential (www.allergen.org) and have been officially recognized and nominated by WHO/IUIS (Subcommittee on the nomenclature of allergens). Modern research has led to the purification of natural and recombinant allergenic proteins from NRL, referred to as Hev b 1, 2, 3, 5, 6, and 15, identified as main allergens of *Hevea brasiliensis* (4, 5). The proteins of the rubber particles comprise the two main allergens Hev b 1 and Hev b 3, both strongly associated with latex allergy in SB patients (6) (Table I). Other proteins are also found in the latex, which play major allergens but with important cross-reactive properties towards foods (Table II).

Table III. *Latex proteins and cross-reactivity*

Major Allergen	**Characteristics**
Hev b 8 (15 kDa)	An allergenic protein aspecific latex also present in all eukaryotic cells. It is equipped with a high level of similarity with the other profilins, however it contains certain uncommon epitopes. Hev b 8 is an important mediator of cross-reactivity between pollen and common fruits, or exotic or tropical fruits. In view of the panallergenic nature of profilin, recognition of IgE anti Hev b 8 should not be taken as proof of primary sensitisation to latex.
Hev b 11 (32 kDa)	An allergenic protein that shows a strong similarity with other molecules of the same family present in fruits such as chestnuts, avocado and banana.

Latex fruit syndrome Hev b 2 (β-1,3-glucanase) PR-2 are enzymes widely spread in the plant kingdom and common epitopes have been identified in the 1-3 β-glucanase of tomato, potato, pepper, banana, latex, Ole e 9 and birch and ash pollen (Palomares, CEA 2005), but also in avocado, chestnut, banana, kiwi, fig (Breiteneder et al. JACI 2000). IgE directed against the protein part of Hev b 2 are found in subjects with food allergy, while those directed against the carbohydrate part of Hev b 2 are found in subjects without food allergy (Breiteneder H, personal communication)

Finally, like profilin Hev b 8, two smaller molecules can create immunological interferences, being ubiquitous proteins in higher organisms as highly cross-reactive panallergens in the plant world. A significant percentage of patients allergic to pollen is sensitized to profilin, giving rise to cross-reactivity serological tests with latex and various common fruits (kiwi, banana) or tropical or exotic fruits (avocado, pineapple) (Table III).

Molecular diagnostics uses the most important latex components by determining allergen sensitization profiles in the different groups of latex allergic patients (7, 8) (Fig. 1). The evaluation of the distribution of latex allergens inside and outside the gloves showed a higher concentration of Hev b 5 and Hev b 6.02 on the inside, while Hev b 1 and Hev b 3 on the outside, confirming a close relationship between the different localization of allergens. This implicates a different sensitization pathway according to the different groups of the population at risk and the resulting selectivity of the IgE specific response (9).

Molecular-specific diagnosis of latex is an important tool to obtain a precise assessment in patients with medical risk, allowing an appropriate strategy of intervention and/or avoidance, significantly reducing the risks and healthcare costs. Serum IgE_tests that use highly purified allergens or recombinant involve less risks for the patient, unlike the prick tests where the patient has a high risk of anaphylaxis. Furthermore, prick tests may be influenced by the assumption of interfering with essential drugs or may not be feasible to people with

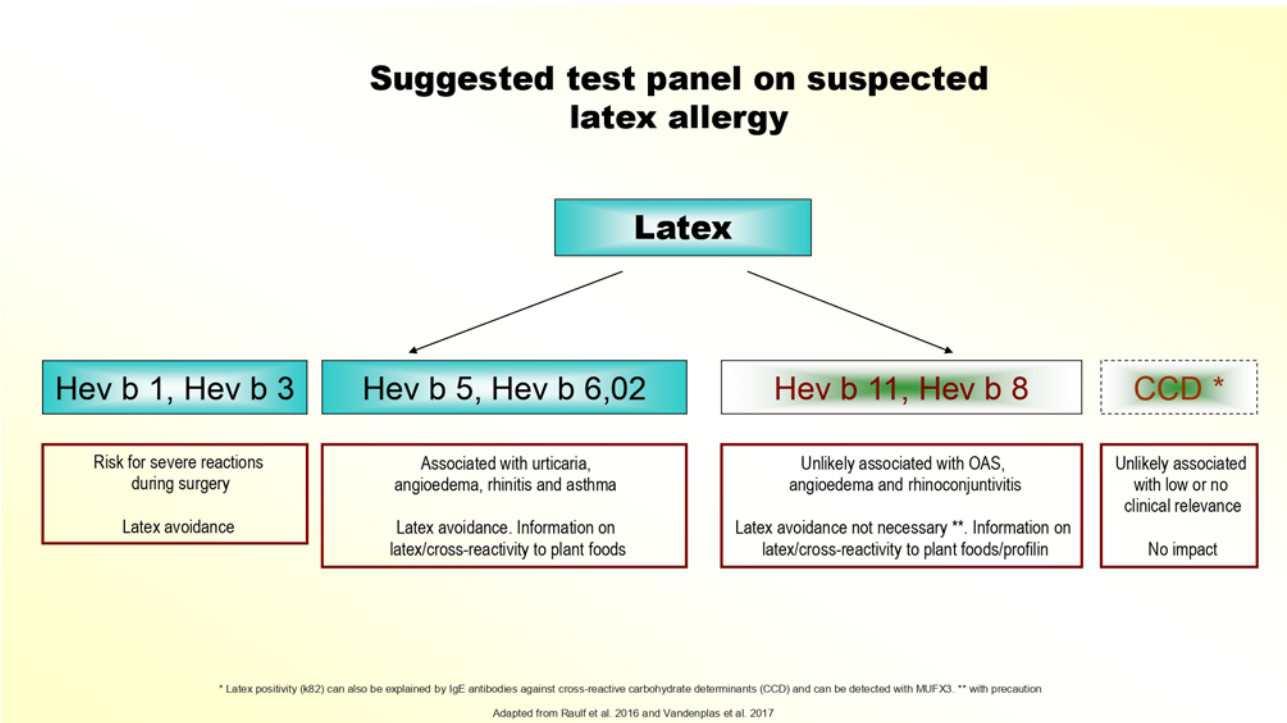

Fig. 1. *The most important latex components*

skin conditions unsuitable for skin tests. Moreover, the development of screening test with multiple or multiplex allergens tests identifies multiple specific IgEs, even for latex recombinants, requiring a small blood volume and making these tests more useful in childhood (10).

In clinical practice the central role of CRD in latex sensitization is currently to distinguish between true allergic disease and a mono-sensitization to profilin. The absence of a clear correlation between specific allergenic proteins and clinical pictures of latex allergy makes CRD of little use in this regard. The preventive identification of subjects predisposed to latex-fruit syndrome based on sensitivity to specific molecules will be more useful in the future.

Undoubtedly, a more accurate diagnosis based on molecular components can better define the patient's sensitization profile, and consequently set up an immunotherapy tailored to the individual patient (patient-tailored immunotherapy) (11).

Precision medicine (PM) represents a potentially more significant relevance in an emerging coronavirus pandemic in order to allow the selection of specific preventive measures. Applying PM premises in an emerging coronavirus pandemic acquires potentially more significant relevance to allow the selection of specific preventive measures and biomarkers that will be useful in disease management (12).

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REFERENCES

1. Vandenplas O, Raulf M. Occupational latex allergy: the current state of affairs. Curr Allergy Asthma Rep 2017; 17:14
2. Panesar SS, Javad S, de Silva D, et al. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy 2013; 68:1353-61
3. Bernardini R, Novembre E, Lombardi E, et al. Risk factors for latex allergy in patients with spina bifida and latex sensitization. Clin Exp Allergy 1999; 29(5).
4. Kurup VP, Sussman GL, Yeang HY et al. Specific IgE response to purified and recombinant allergens in latex allergy. Clin Mol Allergy 2005; 3:11.
5. Raulf-Heimsoth M, Rihs HP, Rozynek P. et al. Quantitative analysis of immunoglobulin E reactivity profiles in patients allergic or sensitized to natural rubber latex (Hevea brasiliensis). Clin Exp Allergy 2007; 37:1657-67
6. Scala E, Alessandri C, Palazzo P, et al. IgE recognition patterns of profilin, PR-10, and tropomyosin panallergens tested in 3,113 allergic patients by allergen microarray-based technology. PLoS One 2011; 6:e24912.
7. Vandenplas O, Raulf M. Occupational latex allergy: the current state of affairs. Curr Allergy Asthma Rep 2017; 17:14.
8. Raulf M. EAACI Molecular Allergology User's Guide. Pediatr Allergy Immunol 2016; 27:1-250.
9. Peixinho C, Tavares-Ratado P, Tomás MR, et al. Latexallergy: new insights to explain different sensitization profiles in different risk groups. Br J Dermatol.2008; 159:132-6
10. Ansotegui IJ, Melioli G, Canonica GW, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organization Journal (2020).
11. Valenta R, Twaroch T, Swoboda I. Component-resol-ved diagnosis to optimize allergen-specificimmunothera-py in the Mediterranean area. J Investig Allergol ClinImmunol. 2007; 17:36-4.
12. Crisci CD, Ardusso LRF, Mossuz A, Müller L. A Precision medicine approach to SARS-CoV-2 pandemic management Curr Treat Options Allergy 2020; 8:1-19. doi: 10.1007/s40521-020-00258-8.