

# Latex Allergy in Children

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Received Date: 4<sup>th</sup> February 2015

Accepted Date: 4<sup>th</sup> March 2015

Published Date: 12<sup>th</sup> March 2015

Citation: Cantani A (2015) Latex Allergy in Children. Enliven: *Pediatr Neonatol Biol* 1(1): 005.

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## Abstract

Although severe anaphylactic reactions are rare, allergic or immediate hypersensitivity reactions to natural rubber latex (NRL) have been reported in children with increasing frequency in the last few years. Indubitably, every-day rubber has been employed in thousands and thousands of products for over a century, while recently NRL allergy has been recognized as a substantial medical problem. Children with spina bifida undergoing multiple surgical procedures, as well healthy babies, appear at high risk for NRL allergy, with life-threatening reactions reported during surgery or while playing with balloons. Skin prick testing is the preferred diagnostic method, especially in the prick by prick version. During procedures, Parents of children with latex allergy should take caution that their babies avoid contact with rubber products, and a latex-free environment. Since minimal contacts with NRL products may produce reactions, the primary treatment for latex allergy is avoidance. The cross-reactions regarding the latex-fruit syndrome have recently widened the number of possible reactions.

**Keywords:** Latex; Latex allergy and anaphylaxis; Spina bifida; Surgical procedures; Latex rubber gloves; Latex-fruit syndrome

## Introduction

It is supposed that the word 'latex' derives from its liquid aspect (from Latin liquid). Spanish explorers discovered native inhabitants of South and Central America who first used latex to make waterproof shoes and bouncing toys for children. However the material, due to the long sea journey to Europe degraded, and consequently nearly fell into oblivion. Joseph Priestly, a British chemist, coined the term "rubber" in 1770 because he first noticed that this compound would "rub" out pencil marks. The medical use of gloves dates back to the asepsis first put into practice by Semmelweis (1818-1865), however only in 1889 Halsted (1852-1922) developed the first latex gloves for his health personnel.

Although NRL is produced by several hundreds of trees, shrubs, and vines, only the NRL from *Hevea brasiliensis* with a 1% from *Parthenium argentatum* (Euphorbiaceae) is commercially exploited [1]. The raw latex as it flows from the tree is composed of natural rubber particles (33%), resin (2%), proteins (1.8%) and water. In addition, to prevent a premature coagulation by microbial growth and to enhance stability during transport a low ammonia-based preservative (0.2%) is added [2]. During NRL preparation, several components are required for glove formulation, such as vulcanizing agents, stabilizers, accelerators, anti-oxidants, etc [1]. The production of NRL-containing items in the whole world, from gloves, balloons and condoms to rubber bands and car tires is about 6 x 10<sup>6</sup>t/year [3].

## The Allergens

From *Hevea brasiliensis*, the allergen Hev b 1 (rubber elongation factor), with a molecular weight (MW) of 14kD has been characterized [4]. In addition, polypeptides in *Hevea* latex are known as the major cause of latex type I sensitivities. A 20kD protein has been recently reported to be a major allergen in latex (prohevein). The IgE-binding capacity of prohevein in latex is mostly attributed to hevein, the N-terminal domain of prohevein. It has been demonstrated that hevein, a 4.7kD polypeptide, is the predominant component in the fraction with latex proteins with a MW smaller than 10kD [5]. An association to HLA-DR phenotypes has also been demonstrated for the sensitization against hevein, therefore a well-defined latex allergen [6]. In health care workers, hevein has been identified as the major latex allergen and is allergenic by inhalation whereas in spina bifida patients the Hev b 1 is the major allergen and is allergenic by direct mucosal contact [4,7].

## Epidemiology

It has been recently stressed that the incidence of NRL hypersensitivity is increasing, with cases even in very young children, between 1.2-1.75 [8,9] and 2 years of age [10]. SPTs (skin prick tests) are positive in 3-6.8% of atopic children [11-13], and the levels of specific IgE antibodies are high, between 12% [14] and 21% [15], especially in children with positive challenges [12]. Sensitization starts in children within the second year of age [11], but the incidence is higher between 3 and 5 years [11,16].

## Risk Factors

A case reported in 1927 was of hypersensitivity against NRL (severe generalized urticaria due to contact from a rubber dental prosthesis) [17]. The prevalence of contact dermatitis (CD) to NRL has rapidly increased following the spread of HIV infection. Therefore all the health care workers at risk, likewise dentists, laboratory personnel, nurses, and non-health care workers, in order to prevent a potential contact with patient body fluids are compelled to wear daily NRL gloves and other protective devices, that causes CD in patients [3]. Similarly there has been a massive increase in the use of NRL condoms and diaphragms, with an alike risk of sensitization [3,18]. An intensive exposure represents the operating rooms for the personnel and nurses, since in addition to NRL gloves, they use NRL masks, catheters, tubes, cannulas, anesthesia/ventilation bags, etc [19-21]. However other risk groups are the rubber industry workers, housewives, customers of restaurants and food stores, as well as the consumers if shopkeepers or craftsmen during their work wear NRL gloves [22]. Additional high-risk subjects are represented in particular by dental patients with NRL prosthesis and especially children subjected to surgical operations, such as those with spina bifida and urogenital malformations, in whom the reactions are frequent, either due to multiple NRL exposures with surgical gloves, or the recurring use of IV sets, tubes, bags, catheters, and RX procedures [23,24].

In a cohort of children and adolescents affected with meningomyelocele, the main risk factors were in addition to the number of surgical operations, atopy and sensitization through exposure to NRL [24-26], but in 60% of cases the reactions took place outside of the operating room setting [9]. In 9.2% of 337 children significant risk factors for hypersensitivity to NRL were, among the underlying diseases, spina bifida (odds ratio 29.2), hydrocephalus internus (10.1), gastrointestinal malformation (5.2) and atopy (2.2). Surgical procedures with significant risk were the implantation of a ventriculo-peritoneal shunt (15.7) and surgery of the gastrointestinal tract (3.1) [27]. Frequency of surgical procedures correlated with risk of hypersensitivity [11,27], above all in NRL-sensitized children [11]. Frequent surgery on atopy was found to have an additional effect on the risk of hypersensitivity [27]. Atopy in particular seems to lower the threshold both for sensitization and for the presentation of clinical reactions [24].

## Routes of Exposure

The exposure to the antigen can occur by cutaneous, percutaneous, mucosal, and in some cases also by parenteral routes [28]. However, if the antigen is aerosol transmitted, the reaction materializes itself within a few minutes and children can manifest rhinitis, wheezing, conjunctivitis, facial angioedema, systemic urticaria and apparent life-threatening events. The NRL allergens in repairable particulate air pollution due to rubbing off tires at the base of asthmatic episodes are not to be overlooked until severe generalized reactions [29].

## Immunopathogenesis

The prevalence of IgE-mediated allergy is high in children with neurological deficits, that of sensitization to NRL attains levels between 18 and 41% [3,26] with peaks as high as 77.1% [9]. The sensitized children are atopic in 49% of cases versus 30% of not sensitized ones, with differences statistically significant as regards the allergic reactions to NRL, respectively in 96% and 30% of cases [23]. (Table 1) [19,28] shows that allergic reaction can develop against an incredible number of disparate objects even of common

usage [16,18,30]. In addition, among the constituents of gloves even cow's milk (CM) casein [31] and cornstarch powder can be found. NRL allergens adhere to this powder used on gloves, and as gloves are used the starch particles, NRL allergens become airborne, where they can be inhaled or come into contact with exposed parts of the body [32]. The immune mechanism mostly demonstrated is IgE-mediated especially in infants and children [9,33-36]. In the serum of patients there are specific IgE antibodies against NRL [28,35], also SPTs, ELISA, RAST, RAST-inhibition are positive; the haptens are always represented by peptides present in NRL [3,37].

## Latex-fruit Syndrome

Recently, a profilin has been identified as a component of NRL, structurally related to profilins of different origin, present in foods and pollens [38], which provoke cases of cross-reactivity among latex, not taxonomically related plants and several fruits (Table 2) [16,34,39-43], in addition to celery and chocolate [36]. About 56% of patients allergic to NRL refer a latex-fruit syndrome [41], including children [44]. Most frequent use of some fruit extracts are reported in (Table 3) [41].

## Allergic Manifestations

Atopy is present in 41-74% of not at risk subjects [9,28,35]. In atopic children it has been evaluated measuring the NRL-specific IgE antibodies: from 0.5 to 10.2% according to specific IgE antibodies lesser or higher than 1.000 U/ml: most children were aware to be NRL-allergic prior to the diagnosis [33]. It is reassuring that only one case of anaphylaxis was reported in 646 operations during a period of 18 years [25]. Two other children developed intraoperative anaphylaxis during intervention [45,46]. The cutaneous exposure induces most frequently symptoms of CD [3,12,28,45], however the latex-fruit and latex-vegetables syndrome may cause in children even anaphylaxis, for example within 5 minutes in a girl holding a balloon [16], facial edema in a child blowing up a balloon [35], and in adults with food allergy [40] or other allergies [47]. In conclusion, most immediate hypersensitivity reactions to NRL are severe, and occur within 10 minutes of exposure [9].

## Diagnosis

In children, to establish the diagnosis of latex allergy, it is crucial to begin with a careful, complete history, the single most important and cost-effective diagnostic tool [3,48]. A clinical history of redness, itching, or swelling, or of unexplained urticaria or anaphylaxis after contact with products containing latex (Table 1) suggests that a detailed history can be an useful tool for the identification of the allergic children.

Both *in vivo* and *in vitro* testing have been employed with varying results *viz.* preferences. Although the allergens Hev b 1 have not been completely characterized, if extracts of demonstrated latex allergen content for testing are at hand, or can be extemporaneously prepared [48], the SPTs are highly sensitive in children with spina bifida and urogenital malformations, but are reliable also in all children [3,12] with positive history due to frequent exposures to NRL [9,35]. SPTs with normal extracts can be used in children allergic to fruits (Table 2) as well as in cases of urticaria, CD and/or anaphylaxis by unknown causes [35]. SPTs can be performed through a latex glove in two phases, the finger test (15 minutes) and the glove test (30 minutes) with positive results in 70% of cases. Screening and diagnosis

may be complicated by the presence of several asymptomatic SPT+ children [12]. Latex-specific IgE appear to be more easily detected in children than in adults [3,9,10]. In children there are additional useful diagnostic methods, such as the patch, the prick + prick [12,16], and the RAST-inhibition tests [3],

also used for investigating cross-allergenicity [49]; the challenge test appear to be correlated to the RAST [12]. CM casein can be an allergen in latex-rubber gloves giving false-positive reactions in non CM-allergic individuals [31].

Table 1: Articles containing latex and number of hypersensitivity reactions in 70 patients

A. Articles that caused clinical and IgE-mediated reactions		
Articles	Patients	No. of reactions (%)
Latex surgical or household gloves	69	43
Sticking plaster	11	9
Balloons	8	6
Bracers	6	5
Contraceptives	5	3
Masks (anesthetic/diving, etc)	3	2
Stretch textiles	3	2
Shoes	3	2
Door/windows isolations	2	1
Air mattress	1	1
Sailing/fishing equipment	1	1
Stamps	1	1
Colours	1	1
B. Articles that caused only clinical reactions		
Articles	No. of patients	
Hot-water bottle	1	
Pacifiers	1	
Shower curtains	1	
C. Additional consumer products <sup>#</sup>		
Additional consumer products	Adhesive tapes	
	Baby bottles nipples	
	Balls and balloons	
	Boots	
	Carpet backing	
	Chewing gums	
	Condoms	
	Diaphragms	
	Diazosensitized photocopy paper	
	Dress padding	
	Dress trimming	
	Elastic bands	
	Elastic or elasticized parts of clothing	
	Elastic stockings and socks	
Foam rubber pillows		
Glue and other adhesive substances		

	Gummed paper, envelope
	Handlebars (e.g., bicycle) and wheels
	Medicine dropper
	Paddles (e.g., ping-pong)
	Pads
	Panty-hose
	Pencil rubber
	Plasters
	Rain wears
	Racquet
	Rubber bands
	Rubber handles
	Rubber key-case
	Rubber soles and heels
	Rubber tyres (e.g., pram, roller-skate, bicycle, wheelchair, etc)
	Shoes
	Shoulder-pads
	Toy balloon
	Toys
	Truncheons
	Tyres
	Water toys
D. Additional hospital latex products <sup>§</sup>	
Additional hospital latex products	Ambu bag
	Anesthesia/ventilation bags
	Bag straps
	Band-aids
	Bands
	Blood pressure cuff and tubing Cannula for IV use
	Catheters (e.g., balloon, rectal, etc)
	Dilatators
	Elastic
	Endotracheal, nasogastric tubes, etc
	Enema kits
	Gastrogavage kits
	Heating/cooling blankets, pillows
	Occlusive dressing
	Orthodontic appliance
	Rubber parts of medical equipment: stethoscope, otoscope, rhinoscope, etc
	Straps for masks
	Tourniquet

<sup>#</sup>Adapted from reference 20

<sup>§</sup>Adapted from reference 29

Table 2: Cross-reactions between latex, fruits, and not fruits in patients with related allergies

Fruits	Apple
	Apricot
	Avocado
	Banana
	Cherry
	Chestnut
	Coconut
	Fig
	Grapes
	Hazelnut
	Kiwi
	Mango
	Melon
	Papaya
	Passion fruit
	Peach
Peanut	
Pineapple	
Not Fruits	Buckwheat
	Celery
	Chocolate
	Potato
	Pistachio
	Tomato

Adapted from references 16,35,40-44

Table 3: Use of extracts of fruits cross-reacting with latex (Table 2)

Foods	Most diffuse use: to tenderize foods (e.g. meat), to Clear drinks (e.g. beer)
	CHYMOPAPAIN and PAPAINE (from papaya)
	Beer
	Cakes
	Coca Cola
	Crackers
	Drinks with fruits
	Fruit juices/salad
	Meat (tenderizes)
	Yogurts with fruits
	Not foods/Other uses
Toothpaste	
Chemonucleolysis	
Cleaners for dental prosthesis and soft contact lenses Drugs: antiphlogistics, laxatives, gastrointestinal Drugs, etc	

Foods	BROMELAIN (pineapple)
	Beer
	Cheese
	Meat
Other uses	Antiphlogistic drugs
	Diet pills
	FICIN (fig)
	Beer
	Cheese
	Meat
	Laxative and deworming drugs
	Leather and textile industry
	OIL of AVOCADO
	Cosmetics

adapted from references 26

### Prophylaxis

The primary treatment for NRL allergy is avoidance. The spread of such allergy has resulted in the advent of universal precautions for alternative barrier protection from blood and body fluids. It has been demonstrated that with consistent prophylaxis [50] even symptomatic patients can be operated without risk of allergic complications or increasing antibodies. Conversely, surgery without strict latex prophylaxis is the main cause of new sensitization and worsening of pre-existing latex antibody levels [8]. As in all preventive measures, there is a primary and a secondary prophylaxis. Recommendation for primary prophylaxis have been suggested [8,50], however the efficacy of primary and secondary prophylaxis still has to be evaluated [8]. Indeed primary prevention is not a trivial task, since the number of latex objects with which we get in touch since birth is incalculable, as shown in (Table 1). As a consequence, secondary prophylaxis that consists in the avoidance of latex products and of the ingestion of cross-reacting foods could obviously be more at hand: from studies till yet reported it appears that reduction in the NRL exposure of sensitized patients is vital [19]. Since there is a wide heterogeneity among NRL gloves, because antigen content varies from brand to brand and from lot to lot [35,37] and even among lots of the same brand [3], allergic patients and surgeons can use non-latex, synthetic gloves [19,37], which however do not have the same barrier qualities and tactile sensitivity of NRL ones [19]. It has been suggested to subject gloves to an increased washing period during manufacturing, and then to sterilization at 1200°C for 1h in saturated steam [51].

Protocols have been issued on how to provide a latex-free environment for hospitalized NRL-sensitive children, especially those undergoing surgery [19,50,52]. For allergic patients it has been recommended the preoperative and intraoperative administration of H1 or H2 antihistamines and/or prednisone, similarly to protocols issued for the prevention of adverse reactions to contrast media [52-54], but only as an adjunct to latex avoidance precautions, being the results often unclear [3]. As alluded to before, accurate preventative measures can insure that symptomatic children can be successfully operated without risk of severe allergic reactions, or anaphylaxis [8]. It is necessary the highest care for atopic children, who are exposed to thousands of consumer products that contain NRL (Table 1), and

become sensitized even by slightest contacts with latex [16,33]: in babies with spina bifida the contacts should be prevented since birth [3]. In particular pacifiers and baby bottle nipples should be banished [19], the surgeons should manipulate the used NRL gloves outside the allergic baby’s room to prevent airborne transmission of latex particles [9], diffused also by corn starch powder on latex gloves and other products [18]. During operations catheters of silastic as well as hypoallergenic tapes and bandages with acrylic adhesive should be preferred [9]. For preventive purposes, diagnosis of NRL allergy should be offered not only to children with multiple operations, or to children who are at high-risk for latex allergy, but also to children with severe AD, fruit allergy and, as already mentioned, with CD, urticaria, or anaphylaxis by unexplained causes [35], and even children with no known risk factor for latex sensitization but with suspected positive clinical history [35,55].

Latex-allergic children should be provided with Medic Alert bracelets and self-injectable adrenalin, and all medical records should show latex allergy [56].

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