

Anaphylaxis: Drug Allergy, Insect Stings, and Latex

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Anaphylaxis is the most severe allergic reaction in humans involving the acute release of mast cell mediators, which can lead to death. Although death is rare, systemic allergic reactions are not uncommon, with an overall estimated risk of anaphylaxis per person in the United States of 1% to 3% [1,2]. A retrospective population-based study of anaphylaxis reviewed 1255 Olmsted County, Minnesota, residents from 1983 to 1987. The occurrence rate of anaphylaxis was 30 per 100,000 person-years, and the average annual incidence of anaphylaxis was 21 per 100,000 person-years [2]. In a retrospective study looking specifically at children and adolescents enrolled in a health maintenance organization from 1991 to 1997, there were 67 cases of anaphylaxis, for an incidence of 10.5 episodes per 100,000 person-years [3]. Atopy is an associated risk factor for anaphylaxis, with two epidemiologic studies observing prevalence to be 37% and 53%, respectively [2,4]. In addition, asthma was reported in 23% of 142 patients with anaphylaxis who presented to an emergency department from 1998 to 1999 [5]. In an innovative approach to studying the epidemiology of anaphylaxis, Simons et al [6] reviewed prescribing patterns of out-of-hospital epinephrine in Manitoba, Canada, and found that overall medication dispensing rates peak in early childhood, and gradually decline with older age. This suggests that anaphylaxis risk peaks in early childhood and dissipates over time. Food allergy

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rates in children decline after the first few years of life and likely parallel this observation.

Food allergy is a significant cause of anaphylaxis throughout life (discussed in more detail elsewhere in this issue). Multiple observations have shown these allergens to be most problematic in childhood but having clear peaks likely related to their prominence in the diet. Pumphrey [7] found that cow's milk allergy resulted in fatal anaphylactic reactions mostly in the first decade of life (youngest 5.5 months, median age 8 years); peanuts in young adults (youngest age 13 years, median age 21 years); and tree nuts in adults (youngest age 18 years, median age 27 years). Overall, fatal food allergy affected younger people than did fatal stinging insect allergy or drug allergy (median age of 21 years compared with 56 or 61 years, respectively) [7].

Although it may be difficult to identify and prevent initial reactions to food, prevention of repeat events is critical. Knowing the allergens that are closely associated with repeat events is necessary. To that end, a prospective study of 432 patients with prior anaphylaxis was initiated to determine which allergens were responsible for anaphylaxis recurrence. A cause of anaphylaxis was identified in 92% of the patients: 61% had food as a cause, 20.4% were caused by venom, and 8.3% by medication. Of the cases that had follow-up data, peanut and tree nuts were the single most common cause for serious and nonserious recurrence of anaphylaxis [8].

Clinical presentation

Anaphylaxis refers to a systemic clinical syndrome resulting from IgE antibody-mediated immunologic release of mast cell and basophil mediators. Although most definitions specify the need for more than one organ system involvement in the syndrome, it is more important to understand the systemic nature of the clinical symptoms. The symptoms typically include some or all of the following: cutaneous (urticaria, flushing, or angioedema); respiratory (either bronchospasm or laryngeal edema); cardiovascular (hypotension, tachycardia, or arrhythmias); gastrointestinal (vomiting, diarrhea); or neurologic (loss of consciousness). A recent retrospective study by Brown [9], of case records from 1149 systemic reactions that presented to an emergency department from 1990 to 1999, looked at the clinical features of anaphylaxis to see if they correlated with severity of anaphylactic reaction. The results showed that a simple grading system of mild (involving skin only), moderate (including diaphoresis, vomiting, presyncope, dyspnea, stridor, wheeze, chest or throat tightness, nausea, vomiting, and abdominal pain), and severe (confusion, collapse, unconsciousness, and incontinence) anaphylaxis correlated well with emergency department physician epinephrine usage. Older age, insect venom, and iatrogenic causes were independent predictors of severity. In children and adolescents, mucosal and cutaneous signs and symptoms were the most common, and occurred in 94% of subjects, whereas respiratory symptoms occurred in 88% [3]. This correlates with

Table 1
Anaphylaxis symptoms: pediatric compared with adults

Symptoms	% Pediatric population ^a	% Adult population ^b
Cutaneous	94	100
Respiratory	88	69
Cardiovascular	21	41
Gastrointestinal	22	24

^a Data from Bohlke K, Davis RL, DeStefano F, et al. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol* 2004;113:536–42.

^b Data from Yocum M, Butterfield J, Klein J, et al. Epidemiology of anaphylaxis in Olmsted County: a population based study. *J Allergy Clin Immunol* 1999;104:452–6.

adult population data [9], where cutaneous features were present in 94% of the patients with anaphylaxis. There are some differences in the presentation of anaphylaxis in the pediatric population compared with the adult population (Table 1), including smaller numbers having cardiovascular signs and symptoms (21% compared with 41%) [2,3]. Other features noted in pediatric anaphylaxis include skin and respiratory signs appearing with an earlier onset compared with gastrointestinal and cardiovascular signs. Most children had a personal history of atopy. The children were usually in the first decade of life, and had atopic dermatitis more frequently with food-induced anaphylaxis. Those with exercise-induced anaphylaxis were older and had histories of urticaria and angioedema [10]. These same authors recently published a follow-up study on these pediatric cases, and children who had atopic dermatitis or urticaria at the time of the original study, or during the follow-up study, were at a significantly higher risk of recurrent anaphylaxis, as were those who had at least one positive skin test to food allergens [11].

A recent review of 30 children less than 18 years of age with a history of cold urticaria revealed that one third of the patients had anaphylactic reactions. These cold urticaria patients had a high prevalence of asthma (46.7%) and allergic rhinitis (50%), with a strong family history of atopic disease of 89.3% [12].

Specific causes for fatal anaphylaxis

Virtually any agent that can induce mast cell mediator release is capable of causing anaphylaxis, but the most common identifiable causes for anaphylaxis are food, drugs, venom stings, and immunotherapy. A retrospective chart review of 55 pediatric cases of anaphylaxis presenting to the emergency department from 1990 to 1994 showed the most common causative agents were latex, food, drugs, and venoms [13]. The incidence and prevalence rates of anaphylaxis also depend on the precipitating cause. There are approximately 150 fatalities from foods each year in the United States, and peanuts and tree nuts account for 94% of the voluntarily reported cases to the national registry [14,15]. β -Lactam antibiotics were implicated in 400 to 800 fatal anaphylactic episodes per year almost

25 years ago [1]. Whether these numbers are still accurate in 2005 is unclear. Venom stings cause at least 50 deaths in the United States, but this is most likely an underestimate, and the true incidence is unknown [16]. Allergen vaccines cause fatal anaphylaxis in approximately 1 per 2,000,000,000 injections [17].

Anaphylaxis to drugs

The risk of drug-induced anaphylaxis increases with age, most likely related to the higher likelihood of multiple drug use [18]. Anaphylaxis or anaphylactoid reactions (non-IgE mediated release of mast cell mediators) include latex, anesthetic agents, radiocontrast media, and antibiotics [13,19,20]. The parenteral use of drugs increases the risk and severity of anaphylactic reactions, and most fatal reactions have occurred with intramuscular or intravenous administration [21,22]. The largest retrospective review of drug-induced anaphylaxis is the Boston Collaborative Drug Surveillance Program, and the results indicated a rate of 1 per 3000 hospitalized patients, with most of the reactions caused by antibiotics [23]. Studies looking at the incidence of penicillin anaphylaxis range from 1.23 per 10,000 injections in children and young adults who were receiving monthly prophylactic penicillin G [24], to 2.17 per 10,000 injections of prophylactic intramuscular benzathine penicillin in healthy military recruits [25]. In the retrospective review of pediatric cases of anaphylaxis by Novembre et al [10], the incidence of drug-induced anaphylaxis was 11%, with nonsteroidal anti-inflammatory drugs causing 50%, antibiotics 40%, and muscle relaxants 10% of reactions. In Dibs and Baker's [13] study, the incidence of medications inducing anaphylaxis was 16%, with antibiotics causing 9%, and other drugs causing 7% of reactions. In Pumphrey's [7] review of fatal reactions, over four fifths of victims of fatal drug anaphylaxis had no previous awareness or indication of their drug allergy.

Penicillin is a small-molecular-weight molecule (hapten) that binds to carrier proteins, and this hapten-protein complex is antigenic. Up to 10% of the population relates a history of penicillin allergy, but in actuality up to 90% of those patients do not have specific IgE, and could use penicillin as safely as the general population [26]. In patients who had convincing histories of penicillin reactions, skin testing with penicillin and some of its metabolites has been reviewed and was found positive in 7% to 63% of those patients. When these patients were then challenged with the medication, the true sensitivity was almost 100% [27]. A report of skin testing and oral challenge in 247 children suspected to have penicillin, amoxicillin, or a cephalosporin allergy resulted in 34% having an IgE-mediated reaction. A total of 32% of 85 suspected penicillin reactions, 34% of 156 suspected amoxicillin reactions, and 50% of 26 suspected cephalosporin reactions were related to an IgE-mediated mechanism. There were no severe reactions with oral challenge after negative skin testing. Because of the risk of recurrent sensitization, however, repeat skin testing was done after the administration of the medication. In fact, there was a 14% rate of recurrence of drug sensitization [28].

For medications that do not have standardized skin test reagents, allergists have used dilutions of the medication in question to try to detect specific IgE reactions. In general, percutaneous skin testing should be done before intradermal testing. The positive and negative predictive values are not known for these nonstandardized tests, however, and a negative result does not exclude an IgE-mediated reaction to that particular medication. Some experts' general impression is that if the native drug caused a positive skin test reaction, and the test was done using nonirritating concentrations, it likely represents the presence of IgE antibodies. Empedrad et al [29] recently published a study of the maximal nonirritating intradermal concentrations of 15 common antibiotics in 25 non-allergic controls. This list may help clinicians with a practical guide in which a positive test result may indicate IgE-mediated disease, and a negative result may provide a reassuring starting dose for desensitization. In patients who have a history of anaphylaxis to a particular drug, avoidance of the drug and use of an appropriate alternative is the first choice for treatment. If there are no other alternatives, however, desensitization to the drug is an option. Drug desensitization is a technique to give gradually increasing doses of the medication presumed to cause the IgE-mediated reaction, until the final dose is tolerated. It is believed to render the mast cells unresponsive to the specific allergen used in the protocol. Drug desensitization protocols have been published for limited antibiotics, such as penicillin (including the β -lactam antibiotics); sulfamethoxazole; and ciprofloxacin [30–32].

Anaphylaxis to stinging insects

Stinging insects are all members of the order Hymenoptera; this includes honey bees, yellow jackets, wasps, hornets, and imported fire ants. The history of the sting can potentially give more information regarding the specific insect, because the location of where the sting occurred and the aggressive nature of the insect may help to identify the insect. Yellow jackets cause most allergic sting-reactions in the United States, and are typically more aggressive than honey bees, who usually only sting when they are provoked. Yellow jackets usually nest in the ground, and are attracted to picnic areas and garbage cans. Hornets are closely related to yellow jackets, but make their paper nests in trees and large shrubs. Wasps also form paper nests in trees, shrubs, and under eaves of buildings. Honeybees are not aggressive by nature, and their hives are large, with multiple stings not uncommon if their hive is disturbed. The honeybee usually loses its barbed stinger after the sting, resulting in its death from evisceration. The Africanized honeybee, whose venom is almost identical to the domestic honeybee, is more aggressive, and their habitat has been spreading northward, including parts of the United States. The imported fire ant was introduced into the United States in the early 1900s in the Port of Mobile, Alabama, and their habitat has now spread beyond the southeastern United States. They build large nests underground or in a mound, which can contain up to 100,000 ants, and are aggressive if their nest is disturbed. The fire

ant attaches with its mandible, and pivots to deliver its stings. They may attack in large numbers, and there have been reports that they have even attacked immobile individuals in nursing homes. This overt aggression usually occurs during periods of drought or floods, where the ants may even search indoors for food. With the recent flooding in southeastern United States, this source of stings may need to be more closely monitored.

The venoms contain proteins, peptides, and vasoactive amines, such as histamine, norepinephrine, acetylcholine, and dopamine [33], and all these components are responsible for the toxic effects of the venoms. Several of these proteins are known to be allergenic, including the enzymes, and mellitin, a protein found in honeybee venom. The typical sting contains 50 μ g of protein.

The incidence of hymenoptera venom allergy in children is approximately 0.4% to 0.8%, and clinical features usually range from urticaria to anaphylaxis. Fatal reactions can occur but with less frequency than in adults because of unclear factors [34].

After a probable cause has been elicited by the history, tests for confirmatory specific IgE may be helpful. Venom testing can be done with skin testing, or with in vitro testing. Because there have been reports that in vitro test results may be positive in 10% of persons who have a compelling history of insect sting reaction, but have negative skin testing results, the Insect Committee of the American Academy of Allergy, Asthma, and Immunology have made new recommendations that skin testing and in vitro testing may be complementary, and may need to be repeated, especially in individuals who have a history of severe reactions, but negative skin tests [35]. The outcomes of allergy to insect stings in children were recently reviewed by Golden et al [36], where they conducted surveys of patients who had previously been treated with venom immunotherapy. Systemic reactions occurred less often in children who had received venom immunotherapy, and there was a lower risk of a systemic reaction even 10 to 20 years after treatment was discontinued. This prolonged benefit also has been seen with adults [37,38]. Venom immunotherapy to yellow jacket has also shown to improve health-related quality of life in patients [39]. In a study measuring postmortem levels of venom-specific IgE in victims of fatal reactions to venom stings, the level of specific IgE antibodies was not predictive of the severity of the anaphylactic reaction [40], and in the review of fatal anaphylaxis by Pumphrey [7], over two thirds of fatal sting reactions had no prior indication of their allergy.

Treatment

Treatment for anaphylaxis is supportive and includes epinephrine as the first-line pharmacologic agent. Lee and Greenes [41] looked at the incidence of biphasic anaphylactic reactions in pediatric patients who presented to their emergency department, and they noted an overall incidence of 6%, with an incidence of significant biphasic reactions of 3% in patients who were admitted

Table 2
Pediatric doses in anaphylaxis

Clinical indications	Route	Dose	Concentration	Frequency
Epinephrine	IM (SQ)	0.01 mL/kg (maximum 0.5 mL)	1:1000	10–20 min
Epinephrine (shock or unresponsive to IM medication)	IV	0.1 mL/kg	1:10,000	5–10 min
Isotonic fluid	IV	20 cc/kg		IV bolus
Glucagon	IV	0.05 mg/kg (maximum 1 mg)		5–10 min

Abbreviations: IM, intramuscular; IV, intravenous; SQ, subcutaneous.

with anaphylaxis. Delay in the administration of epinephrine was associated with an increased incidence of biphasic reactions and unavailability of epinephrine was associated with death [42]. Table 2 lists the dose and route of epinephrine that may be used in the pediatric population [43]. Although intravenous epinephrine in adults is often not used, it may be necessary in children. The preferred initial route of administration is intramuscular unless the patient fails to respond to resuscitation. Significant venous dilation occurs during anaphylaxis resulting in a marked decline in cardiac preload. Failure to see a response to epinephrine by the intramuscular route may actually represent a vascular volume problem. The use of isotonic intravenous fluid may become necessary for volume expansion using a dose of 20 mL/kg that can increase if necessary. Pumphrey [44] noted that in 10 cases of fatal anaphylaxis where postural information was available, the patients died in the upright position, and 4 of the 10 deaths occurred within seconds of the patient being moved from the supine position to the upright position. His explanation is that physiologically, during shock there is insufficient venous return, and by moving to the upright from the supine position, there is resultant loss of cardiac filling, leading to circulatory collapse. Raising the legs while the patient is supine (Trendelenburg's position) may increase blood flow to the heart, and possibly improve outcome.

Although glucagon has been advocated in patients with β blockade, the efficacy in children requires study. The usual dose is 0.05 mg/kg as a bolus in children and may be used as a continuous drip at the same dose per hour. Glucagon raises intracellular cyclic AMP by a mechanism independent of β receptors. Preventative treatment for anaphylaxis includes patient and family education on avoidance of the identified agent and use of self-injectable epinephrine.

Latex allergy in children

Anaphylaxis to natural rubber latex (NRL) became one of the most pervasive problems in medical and surgical care in the early 1990s in children with spina bifida (SB). A case report by Slater [45] and subsequent recognition of an epidemic cluster of severe, life-threatening allergic reactions in the operating

rooms at the Children’s Hospital of Wisconsin led the Centers for Disease Control and Prevention to recommend that all elective surgery in the United States on this patient population be curtailed. Investigation into this cluster of allergic reactions found that latex allergy was the likely inducer of these reactions and a concerted effort on prevention of latex allergic reactions took place in the world. Guidelines to avoid latex allergen in hospital settings and community settings for those allergic individuals have led to significant reductions in these untoward reactions, especially in the operating room. The initial cluster of allergic reactions identified that one of every eight children with SB had life-threatening reactions in the operating room without latex precautions over a 12-month period, which was nearly 500-fold higher than the expected rate of allergic reactions during anesthesia [45,46]. Although adult health care workers were starting to be recognized as a significant risk group for development of latex allergy, it was a concerted effort by clinicians, researchers, latex manufacturers, government, and allergy societies (especially the American College of Asthma Allergy and Immunology and American Academy Asthma Allergy and Immunology) alerted by this potentially fatal problem that led to a very successful public health approach to nearly eliminating this risk.

Natural rubber latex

NRL is an intracellular cytosol derived from the rubber tree *Hevea Brasiliensis*, one of over 2000 lactifer-type plants in the world belonging to the family Euphorbiaceae (Table 3). Lactifer plants are unique because they contain cells that secrete a milky substance (NRL) that circulates in branched tubes. These tubes penetrate the tissues of the plant in a longitudinal direction to conduct various substances and act as a secretory reservoir. In the case of the rubber tree, the NRL is rich in *cis*-1,4-polyisoprene that cross-links to form a natural plug, which mends a cut in the surface of a lactifer plant similar to a fibrin clot in human skin wounds. Manufacturers have taken advantage of the

Table 3
Plants of the Euphorbiaceae family

Common name	Genus / species
Natural rubber tree	<i>Hevea brasiliensis</i>
Chenille plant	<i>Acalypha hispida</i>
Crown of thorns	<i>Euphorbia milii</i> var <i>splendens</i>
Tapioca plant	<i>Manihot esculenta</i>
Jacobs coat	<i>Acalypha wilkesiana</i>
Poinsettia plant	<i>Euphorbia pulcherrima</i>
Castor bean	<i>Ricinus communis</i>
Mexican fire plant	<i>Euphorbia heterophylla</i>
Medusa’s head	<i>Euphorbia caput-medusae</i>

constituents of NRL by developing numerous indispensable rubber products. There are numerous components of NRL, of which the most important to this discussion is the 2% level of water-soluble and membrane-bound proteins. The other components include organelles, organic material, water, electrolytes, lipid, and carbohydrate. It is these heat-stable proteins, however, which have resulted in the two-decade epidemic of life-threatening allergy to proteins retained in finished NRL products that has captured the attention of manufacturers, physicians, scientists, government regulators, attorneys, and patients around the globe [45–82].

Children at high risk of latex sensitization and allergy

The largest prevalence study published of unselected (not at a specific clinic for a specific problem related to allergy) children (>1000) evaluated for latex allergy by skin testing demonstrated that less than 1% are skin reactive to NRL. More important is that the eight children who were skin test-positive were asymptomatic when recalling situations of contact with NRL [77]. A second study of the largest group of selected (patients referred to a dermatology clinic) children (>3000) also demonstrated a low prevalence of skin test reactivity (1.1%) to NRL. This does not seem to be significantly different from the study of unselected children [78]. In contrast, however, most of these skin test-positive children were symptomatic. A smaller case series in United States children showed skin test reactivity to NRL in approximately 3% of the population but the sample size was too small to draw any definitive conclusions [79].

In contrast, two blood donor studies of adults using serologic testing alone found circulating anti-NRL IgE antibodies in 6% of the blood samples [83,84]. Given the current sensitivity and specificity of available serologic testing, without confirmatory medical histories or skin tests, standard bayesian statistical calculation confirms that the rate of false-positive serum tests is significant in populations where there is a low prevalence of disease. In fact, screening the general population for NRL allergy by a blood test is not recommended for this reason [85,86]. Although it is possible that these studies represent identification of true-positive tests, it is more likely that the blood donor studies represent over identification of subjects or false-positive tests.

Children with SB are at high risk of developing latex allergy. In one study, 68% of children with SB were skin test positive [46]. These individuals present with a unique set of circumstances that gives insight about risk factors for NRL allergy. Most patients with SB undergo at least two operations (spinal defect repair and ventriculoperitoneal shunt for hydrocephalus associated with an Arnold-Chiari malformation) in the first 2 weeks of life. Multiple specialty surgeries (orthopedic, neurosurgery, and urology) are frequent in these patients because of concurrent problems from hydrocephalus, paraplegia, and neurogenic bladder. Compromised bladder contractility and bowel motility may lead to a need for repetitive bladder catheterization and manual rectal stool disimpaction.

The highest risk factor for development of NRL-induced anaphylaxis in the operating room in one SB study was the need for daily rectal disimpaction. The implication of this was that NRL gloves used in the past contact mucosal surfaces that allow absorption of latex antigen and sensitization.

Some studies suggest this population of SB patients may be highly atopic [46]. A recent study reconfirms that the independent associations of multiple surgeries (more than four) and elevated IgE antibody is associated with latex allergic sensitization in patients with SB [87]. A neural immune mechanism predisposing to the development of allergy has been postulated. Spinal cord-injured patients, however, were shown not to be at risk for development of NRL allergy [61]. Because the actual routes of exposure are multiple (skin, bladder, neural, peritoneal, mucosal) and the timing of the development of NRL allergy in this population is variable, it is recommended that these patients be handled with no direct contact to NRL from the time they are born. The routine handling of patients with SB with latex free or latex safe equipment has now led to safe management of these individuals' medical care [88].

Although children with the congenital abnormality of SB are clearly at increased risk of latex sensitization, other children are also at risk. Previous studies have suggested that multiple surgeries are an independent contributing factor to the development of NRL allergy. A critical study implicates that any previous operation (not just those with multiple operations) placed the patients at risk for sensitization to NRL protein [89]. The odds or chance of latex sensitization was 13 times higher in any subject who had had a previous surgical operation. Interestingly, each additional operation poses a 2% risk of further subjects becoming sensitized. This observation is further refined and confirmed by another German study where repeated operations in the first year of life strongly predicted the development of latex sensitivity [90]. This study raises significant concerns about the use of latex precautions in operations in children during their first year of life because all of the sensitized subjects in this study actually had an operation in the first year of life. Documentation of neonates developing

Table 4
Children at risk of natural rubber latex sensitization and allergy

Diagnosis	Risk ^a
Spina bifida	High
Surgery in the first year of life	High
Urogenital malformations	Medium to high
Multiple surgeries	Medium to high
Neurogenic bladder	Medium
Atopic	Medium
Premature neonates	Medium
Hydrocephalus	Medium
Spinal cord injury	Low to medium

^a Risk: A category of low, medium, and high risk are estimated based on medical literature prevalence by the author. Low designates those equal to the general population of 1%. Medium is greater than the 1% but less than 10%. High is considered in those diagnoses with >10% prevalence.

sensitivity in newborn nurseries suggests that primary prevention may need to broaden from patients with SB to all neonates. The known risk groups are characterized in Table 4 but may include others where the risk is not determined but could be characterized as having similar clinical circumstances.

Biologic properties of specific latex allergens affecting children with spina bifida compared with adult health care workers

Centrifugation of NRL, frequently performed to concentrate the isoprene particles, results in separation of NRL into three distinct layers. The bottom fraction contains luteoids or organelles of the latex, and seems not to have significant contributions of latex allergenic proteins. The center fraction (C serum) contains many water-soluble proteins, whereas the top layer is rich in rubber particles. These rubber particles have distinct sizes with varying quantities of membrane-bound allergens. Hev b 1 is mainly found on large particles greater than 350 nm in diameter, whereas Hev b 3 is found on small particles less than 70 nm in diameter. Different allergens concentrate in these various layers. This is of interest because children with SB seem to react almost exclusively to Hev 1 and Hev b 3. Hev b 7 has also been identified as a unique allergen in these children but not to the extent of the membrane-bound proteins [91]. There have been 13 proteins characterized and accepted by the World Health Organization–International Union of Immunological Societies allergen nomenclature committee as latex allergens. The next sections concentrate on a few of the proteins that are most relevant in children.

Hev b 6 (prohevein)

Hev b 6 shows strong reactivity with IgE from health care workers and SB patients with latex allergy. Prohevein and hevein make up a large percentage of the allergenic proteins in latex. In immunoblot and ELISA, the 43 amino acids–long N-domain of prohevein seemed to exhibit IgE binding with significantly higher number of latex-sensitized patients compared with the 144 amino acids–long C-domain of Hev b 6. The results of skin test reactions correlated well with the in vitro IgE to latex allergens. Epitope mapping of the prohevein molecule revealed more IgE binding regions near the N-terminal end of the protein [91].

Hev b 7

This patatin-like protein shows IgE binding reactivity with 23% of health care workers with latex allergy. Although both health care workers and SB patients exhibited IgE binding with Hev b 7, this allergen recognized only a small group of patients, for whom IgE antibody against other major latex allergens could not be detected [92].

Hev b 1 (rubber elongation factor)

Rubber elongation factor has been purified and cloned as a 137–amino acid protein. The native protein appears as a tetramer of molecular mass of 58 kd. Hev b 1 is a major allergen reacting with 81% of latex-sensitized SB patients and 50% of health care workers. In a multicenter study using radioallergosorbent and ELISA assays, 13% to 32% of health care workers and 52% to 100% of SB patients with latex allergy showed strong IgE binding with Hev b 1 [91].

Hev b 3

This protein is associated with the small rubber particles in latex and demonstrates a strong IgE-binding reactivity in SB patients with latex allergy. The reactivity of Hev b 3 with serum IgE in health care workers is less frequent and weaker than in SB patients. The amino acid sequence comparison of Hev b 3 demonstrated 47% sequence homology with another major allergen, Hev b 1, a component of large rubber particles. In ELISA inhibition, Hev b 1 preincubated latex allergic sera exhibited more than 80% inhibition in IgE binding to the solid phase coated Hev b 3 indicating the presence of similar conformation in these proteins [91].

Latex allergy and food reactions

Many investigations have shown clinical allergic reactions of several fruits and vegetables in patients with documented latex allergy. The foods most frequently resulting in clinical reactions are avocado, kiwi, banana, and chestnut. Multiple “stone fruits” (peach, cherry) and other foods (fig, melon, pineapple, celery, cantaloupe, apple, pear) may cause immunologic cross-reactivity in immunoassays but result in fewer clinical symptoms.

Primary prevention and unique circumstances in the care of high-risk children

Since the first reports of anaphylaxis in children with SB, primary prevention by avoidance of contact of latex, especially dipped medical products like gloves and urologic latex catheters, has been the mainstay of therapy. IgE-mediated reactions may be reduced in severity but are not prevented by pretreatment with steroids and antihistamines in operating room settings [93]. Preventive measures through reduction of contact are summarized in [Box 1](#). There may be unique issues in each institution that provides care for these special children. A latex allergy committee to work on policies and procedures is necessary to provide comprehensive multidisciplinary safe care. Whether it is necessary that all chil-

Box 1. Prevention of latex allergic reactions in children with natural rubber latex sensitivity

No skin or mucous membrane contact with latex-dipped products during surgery^a

Synthetic gloves used

Remove top of multidose vial to draw up medication

No in-line latex valves in intravenous tubing

No prepackaged kits with latex gloves (eg, suction or bladder catheter kits)

No balloons or other latex products in the area

No latex tourniquets

^a Institutions that use powder-free low-allergen gloves should not need to schedule special times, such as the first case of the day in the operating room, because no aeroallergen is expected. Those institutions that use powdered latex gloves should schedule cases as the first case of the day where no powdered gloves have been used or stored since the prior day.

dren and neonates under the age of 1 have latex avoidance during surgery is unclear and requires further investigation.

Children with latex allergy should have access to epinephrine at school, home, and other at-risk places. Ensuring that gloves in nursing offices at schools are safe and no powdered balloons are in schools is difficult but necessary and the physician should advocate by letter writing and contact with the school to avoid untoward reactions.

With the advent of lower-allergen NRL materials, latex precautions, and medical awareness, the epidemic of latex allergy seems to have been controlled. Continued vigilance and standards ensure the prevention of another epidemic.

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