

Continuing Medical Education

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Latex allergy

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Latex allergy is an important medical problem for an increasing number of patients. Type IV hypersensitivity reactions to latex products, typically associated with chemicals added to latex during processing, have been reviewed elsewhere.¹ Type I, or immediate hypersensitivity reactions, were first reported in Germany in 1927.^{2, 3} The next published case appeared 52 years later,⁴ and the earliest North American reports were published simultaneously in 1989.^{5, 6} Over the next 4 years, the U.S. Food and Drug Administration (FDA) received over 1100 reports of injury, and 15 deaths, associated with latex allergy.⁷ In this article, I review the current understanding of latex allergy and the treatment of this condition.

BACKGROUND

The origins, biosynthesis, and uses of natural rubber latex have been discussed elsewhere.^{1, 8} Natural rubber (*cis*-1,4-polyisoprene) is a processed plant product, over 99% of which is derived from the latex, or milky sap, of the commercial rubber tree *Hevea brasiliensis*. Vulcanization is a process by which latex is heated in the presence of sulfur, during which the elasticity and thermostability of rubber are vastly improved.⁸ Latex is a complex intracellular product, the essential functional unit of which is the rubber particle, a spherical droplet of polyisoprene

Abbreviation used

FDA: Food and Drug Administration

coated with a layer of protein, lipid, and phospholipid. Among these surface proteins is prenyltransferase, which is found both free in the cytosol and in association with the rubber particle.⁹

Rubber biosynthesis appears to occur in the following sequence.¹⁰ Three acetyl coenzyme A molecules are converted into hydroxymethylglutaryl coenzyme A, which is in turn reduced to mevalonic acid, and phosphorylated and decarboxylated to the five-carbon isopentenyl diphosphate. This "isoprene" subunit forms the backbone of monoterpenes (2 isoprene units), diterpenes (4 isoprene units) and sterols (6 isoprene units). Prenyltransferase in several species can generate polymers as large as 10⁵ d; *Hevea* rubber ranges up to 10⁶ d. Some workers have suggested that a "rubber elongation factor" is tightly bound to rubber particles and allows prenyltransferase, which normally condenses fewer than 3 isoprene units, to elongate polyisoprene chains to lengths that run in the thousands in latex-producing species. Both rubber elongation factor (14 kd) and prenyltransferase (38 kd) have been purified; rubber elongation factor has been sequenced as well.¹¹⁻¹⁴

Mature, cultivated *H. brasiliensis* trees are tapped for latex, usually on alternate days. Ammonia, which is often added to latex as a preservative, disrupts the rubber particles and produces a two-phase product that is about 30% to 40% solids. This is typically concentrated to 60% solids, producing ammoniated latex concentrate, which contains 1.6% ammonia by weight. Low ammonia latex concentrate, containing 0.15% to 0.25% ammonia, is also available. At a low ammonia concentration, however, a secondary preservative is necessary to avoid coagulation and

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contamination. Secondary preservatives may include sodium pentachlorophenate, tetramethylthiuram disulfide, sodium dimethyldithiocarbamate, and zinc oxide.

Latex concentrates are used for the production of dipped products, adhesives, foam, and carpet backing. Dipped products include gloves, balloons, and condoms. In dipping, porcelain molds are first coated with a coagulating salt (such as calcium alginate) and then dipped into the already vulcanized latex concentrate.

PATHOPHYSIOLOGY

Immediate hypersensitivity reactions have been elicited by exposure to rubber gloves, condoms, barium enema catheters, bladder catheters, balloons, rubber dental dams, toys, dental prophylaxis cups, and sports equipment. The clinical manifestations of these reactions include systemic urticaria, rhinitis, conjunctivitis, bronchospasm, and anaphylaxis. These immediate hypersensitivity reactions have been shown to be IgE-mediated by skin testing, basophil histamine release, RAST, ELISA, and IgE immunoblots^{4-6, 15-17} and are nearly always elicited by peptides present in natural rubber.

In a recent study investigators were unable to detect latex-specific IgE in 13 of 14 adults with isolated contact urticaria to latex.^{18, 19} This is in contrast to several prior reports in which patients with contact urticaria to latex were found to have positive latex skin test or RAST results.^{4, 20-22}

Latex proteins

The protein content of natural rubber varies with different lots and production methods.^{8, 23} In most investigators' experience, antigen is readily elutable from latex gloves, condoms, and catheters under mild, physiologic conditions, such as those produced by soaking items in a neutral saline buffer at 37° C for 1 to 2 hours. In gloves antigen appears to be asymmetrically distributed across the latex film, with a higher concentration of protein antigen on the outside²⁴ or inside²⁵ of the glove. This is due to the practice of cleaning the glove by soaking (or "leaching") it while it is still on the mold, which results in uneven removal of elutable protein.

Antigen content may be estimated by measurement of total protein or by immunospecific assays with either human or animal antisera. Total protein estimates by standard techniques have a high degree of variability and interference by nonprotein substances coeluted from latex products. Fur-

thermore, the measurement of a particular protein typically depends on the binding or generation of a chromophore to component amino acids, which may be present in minimal amounts in a particular antigen. A target antigen may therefore be "invisible" to a particular assay. For example, Boyle et al.²⁶ found that a 10 kd latex antigen bound poorly to Coomassie Brilliant Blue (Imperial Chemical Industries, Ltd., Macclesfield, Cheshire, U.K.). Although this band appeared clearly in immunoprints in which patient sera were used, it was absent in a standard Coomassie Blue-stained preparation. Tomazic et al.²⁷ have found that both the Lowry and Bradford (Coomassie) assays can measure latex protein reproducibly, but they obtained the most reliable results with ovalbumin as the standard, rather than the more usual bovine proteins. The most successful immunochemical measurements of latex antigens have been RAST inhibition studies²⁸⁻³¹; the only practical limitations to these investigations is the availability of reliable and representative sera and the technical time required, usually 4 days. Polyclonal³² and monoclonal^{33, 34} animal antibodies to latex have also been developed. We have used a mouse monoclonal antibody to latex to detect latex antigen; the advantages are shortened assay time and an inexhaustible supply of antibody. The assay correlates well with RAST inhibition, but the sensitivity is lower (125 ng/ml vs 3 ng/ml by RAST inhibition).³³

With these methods, latex protein antigens have been detected in gloves, catheters, condoms, latex enema cuffs, balloons, and anesthesia circuitry. The range of antigen content is great, at least 400-fold among different brands of disposable gloves. Antigen has been detected in latex baby bottle nipples by crossed radioimmunoelectrophoresis and dot blot^{35, 36} but not by RAST inhibition²⁹; in the latter study, antigen was detectable in a vial stopper, but only after 40 needle punctures. An attempt at *in vivo* detection of antigen in syringe stoppers yielded equivocal results.³⁷

Several approaches have been used to identify the peptide(s) responsible for immediate reactions^{15, 22, 23, 38-49}; peptides ranging in molecular weight from 2 to 100 kd may be involved. Most investigators use either finished products or latex as the antigen source for these studies. My laboratory has shown that an extract from high ammonia latex concentrate is an extremely poor source of material for immunochemical studies. This is probably due to protein hydrolysis, which

occurs in a highly alkaline environment. In contrast, a nonammoniated preparation was shown to produce definite peptide bands, with characteristic and reproducible IgE immunoblotting patterns. Our study suggested that a 14 kd peptide was the most important antigen, at least in children with spina bifida.⁴⁴ In a more recent study, Alenius et al.⁵⁰ found that although most patients with spina bifida who have latex allergy have IgE specific for 14, 20, and 27 kd peptides, the IgE of health care workers with latex allergy typically recognizes only the 20 kd peptide. Thus the antigens that are recognized depend not only on the antigen source material but also on the patient population from which the detecting serum is obtained.

Some investigators have addressed the important issue of the relative antigen content of unprocessed latex compared with glove extracts. Most studies use the more readily available gloves as a source of antigen; others have used raw latex, latex "compound" (low or high ammonia concentrate), or fresh frozen latex. In general, glove extracts contain fewer identifiable peptides than unprocessed latex. Although some reports have produced evidence for the greater allergen potency of raw latex extracts,⁵¹⁻⁵³ two other careful studies have shown that the use of certain glove extracts, rather than raw latex, can improve the sensitivity of in vitro assays for latex-specific IgE. Hamilton et al.¹⁹ have articulated the hypothesis that certain glove products may have "a more complete repertoire" of relevant antigen than crude latex, and Kelly et al.⁵⁴ have suggested that this may be due to new epitopes produced or exposed during processing. The formation of neoantigens during glove manufacturing has also been supported by the appearance in glove extracts of an 11 kd band not present in latex extracts prepared under similar conditions⁴⁵; the same group subsequently identified this novel band in "aged" ammoniated latex.⁵⁵ The appearance of new antigens with processing is not the only explanation for these observations, however. An alternative explanation is that ammoniation and perhaps other aspects of glove production effect the hydrolysis of larger epitope-bearing proteins into smaller epitope-bearing peptides. This and the possibility that latex antigens may be more stable to heat and alkaline denaturation than other *Hevea* proteins might result in a significant enrichment of the epitope content of glove extracts over raw materials, without the generation of new epitopic sites.

Routes of exposure

Latex antigen exposure can occur by cutaneous, percutaneous, mucosal, and parenteral routes; the antigen can also be transferred by direct contact and aerosol transmission. Aerosol transmission of antigen has been suggested in some studies^{56, 57} and documented in two case reports.^{58, 59} In one study a 10 kd antigen could be demonstrated in glove powder by IgE immunoblotting.⁴¹ Jaeger et al.⁴⁷ have produced the most compelling evidence yet that latex antigen is adsorbed to the constarch with which most gloves are dusted for lubrication. Inhalative provocation of 18 patients with latex allergy resulted in symptoms in all patients and increased airway resistance in five. In contrast, constarch-dusted nonlatex gloves elicited only minimal reactions.⁴⁷ In another study the amounts of latex antigen measured in air samples from different areas of the Mayo Clinic correlated well with the frequency of glove use and glove changes in those areas.²⁸

Although severe systemic reactions have occurred after cutaneous and respiratory exposure,^{6, 60-62} it is clear that direct mucosal and parenteral exposure post the greatest risk of anaphylaxis. Several reports highlight the hazards of latex exposure for patients with previously mild (and easily manageable) cutaneous or respiratory reactions, who experience more severe reactions with mucosal or parenteral exposure.^{16, 63-67} All of the deaths caused by latex allergy reported to the FDA have been associated with barium enemas; latex-containing barium enema catheters were recalled in 1990 and replaced with synthetic devices.^{7, 17, 68}

Risk groups

Latex allergy occurs for the most part in well-defined risk groups. These include health care workers, rubber industry workers, and children with spina bifida (meningomyelocele) and urogenital abnormalities. The only common feature among these groups appears to be a high degree of exposure to natural rubber. Health care and rubber industry workers are exposed during the course of their occupations, and patients with spina bifida through repeated surgery and, in some cases, fecal disimpaction and the repeated introduction of a latex catheter into the bladder.

The prevalence of type I latex allergy in the general population is unknown, although the risk appears to be higher among atopic than among nonatopic individuals. Shield and Blaiss⁶⁹ found that 3 of 44 atopic children had positive epicuta-

neous skin test responses to a latex glove extract; none of these children had histories of latex-associated reactions, and none of the 36 non-atopic children tested had a positive skin test response to latex. Among employees in a university hospital in Finland, 1 of 130 (0.8%) non-health care workers was found to be allergic to rubber as determined by prick test and challenge.⁷⁰ In the series of latex-associated anaphylaxis cases reported by Ownby et al.,¹⁷ none of the six patients (including one who died) belonged to any identified risk group.

Health care workers appear to have a 5% to 10% risk of latex allergy. In Finland 15 of 512 (2.8%) workers in clinical units and laboratories were allergic to latex; the highest incidence of latex allergy (4 of 54 or 7.4%) was found in operating room physicians.⁷⁰ Lagier et al.⁷¹ found positive skin test responses and symptoms in 21 of 268 operating room nurses in Marseille. During 1991, 49 health care workers at Mayo Medical Center were referred to the Allergic Diseases Department because of possible latex allergy; 36 had rhinoconjunctivitis and 13 experienced bronchospasm during latex exposure. Of these, 34 had positive skin test results and 19 had a positive latex RAST result.⁷² A worldwide survey of all active-duty dental officers in the U.S. Army in 1990 suggested a prevalence of latex allergy of about 8.8%, although as many as one third of the reported reactions may have been type IV.⁷³

The only study of occupational exposure other than health care settings appeared in 1990. Tarlo et al.⁵⁷ found that 3 of 81 workers in a Canadian surgical glove factory had occupational asthma, based on positive skin test results and spirometric deterioration in the workplace; 7 of 81 reported urticaria at work, but the latex skin test results in this group were not reported separately.⁵⁷

The prevalence of IgE-mediated latex allergy in children with spina bifida is much higher. As case reports appeared in the medical literature,^{5, 64, 74} surveys confirmed an alarmingly high rate of sensitization. The New England Myelodysplasia Association surveyed 187 families in five myelodysplasia clinics and found that between 18% and 28% of patients experienced acute allergic reactions of latex products.⁷⁵ In a subsequent survey of myelodysplasia clinics in 16 Shriners Hospitals (a total of 2925 children), between 0% and 22% of children in each clinic were believed to have latex allergy; the clinic reporting the 22% prevalence was the only one in which most of the families were directly interviewed. Twenty-two children

(15% of those reporting latex allergy) had experienced intraoperative anaphylaxis.⁷⁶ A serologic survey of patients with spina bifida revealed that 35 of 93 (37%) had latex-specific IgE as determined by RAST. Of these, 8 of 35 had histories suggesting clinical latex hypersensitivity; only 1 of 58 patients with negative RAST results gave such a history.⁷⁷ In addition, children with other conditions requiring frequent surgery may be at risk.⁷⁸ These conditions include bladder exstrophy, cerebral palsy, and Dandy-Walker cysts.

Several reports have highlighted clinical and immunochemical cross-reactivity between latex and banana, chestnut, avocado, and other fruits.⁷⁹⁻⁸⁶ So far, all investigations have suggested that *in vitro* cross-reactivity is partial; in addition, RAST inhibition does not necessarily predict clinical sensitivity. It is not yet clear whether patients allergic to fruit constitute an independent risk group, because no published studies address the issue of latex sensitivity in a cohort of these patients. In my laboratory we examined sera from six adults and five children with banana allergy and no clinical evidence of latex allergy. All 11 had positive banana RAST results, with good inhibition by banana extract. Five of six of the adults' sera, but only one of five of the children's sera, demonstrated inhibition of IgE binding to banana RAST disks by latex extract (Osleeb CA, Slater JE. Unpublished data). Larger studies will be needed to assess the prospective risk of latex sensitivity in this group of patients.

As yet, there are no population-based prospective studies that address the natural history of latex allergy. In my experience health care workers appear to have a progression of occupational symptoms, from cutaneous reactions to rhinoconjunctivitis to bronchospasm and anaphylaxis. In addition, the presence of measurable latex-specific IgE may precede the development of clinical symptoms by months or years. Several investigators have commented on the high prevalence of latex-induced contact dermatitis in health care workers with type I latex allergy.^{16, 18, 87} The significance of this observation is not clear, because we do not know the prevalence of latex-induced contact dermatitis in the population of health care workers as a whole.

DIAGNOSIS

The identification of patients at risk is an essential step before medical procedures that entail latex exposure are carried out. The most impor-

tant step in this process is the ascertainment of risk group status, which includes the presence of spina bifida or congenital urogenital abnormalities or employment in the health care or rubber industries. In addition, patients should be asked about a history of latex-associated reactions. Allergic reactions of unknown cause should be discussed and evaluated thoroughly. Unfortunately, even careful history taking will not identify all patients who subsequently react to rubber.

Testing requires the availability of reliable, antigen-containing preparations. Sources of testing materials have included gloves, ammoniated latex, nonammoniated latex, and *Hevea* leaves.

Latex gloves are readily available and inexpensive. Extracts have been prepared by washing and soaking premeasured amounts of glove material in diluent solutions for various lengths of time. Skin tests may also be performed "through" a latex glove.²¹ Because glove antigen content varies from brand to brand²³ and perhaps from lot to lot, the most reliable extract would be derived from the same lot of gloves that caused the reaction. Alternatively, a single, highly antigenic extract may be prepared in large quantities and frozen in small aliquots until use.^{19, 88}

Ammoniated latex is also readily available and inexpensive. The high ammonia preparation contains only unvulcanized latex, ammonia, and ammonium laurate. Extracts may be prepared by centrifugation and filtration to remove polyisoprene and dialysis to remove the ammonia salts and to neutralize the pH.^{5, 17} Others have simply diluted ammoniated latex in neutral buffers with excellent results.¹⁶ Because all dipped products, including latex gloves, are derived from ammoniated latex, one would expect all relevant antigens to be present in ammoniated latex, unless neoantigens are created as a result of the vulcanization process (see above).

Nonammoniated latex and *Hevea* leaves are available only through specialized sources. Both can be used as antigen sources for testing^{5, 89} but are most useful for immunochemical studies requiring intact proteins. FDA and commercial extracts have been derived from various nonammoniated latex preparations.

Skin testing has been performed with extracts derived from each of the above materials. In all studies epicutaneous testing appears to be quite sensitive, especially when two or more source materials are used.^{21, 39, 88, 90} Moneret-Vautrin and Laxenaire⁹¹ have produced the largest serial evaluation of latex skin test results. Among 907

health care workers, 18 were thought to be allergic to rubber as determined by questionnaire. All 18 had positive skin prick test results with "pre-vulcanized" latex. Of the 889 patients with negative histories, only six had positive skin prick test results; one of these six was subsequently shown to be allergic to rubber by challenge. Thus in this series epicutaneous testing was 100% (18 of 18) sensitive and 99% (883 of 889) specific. The predictive value of a positive test result was 80% (19 of 24), and the predictive value of a negative test result was 100% (883 of 883). In the series reported by Lagier et al.,⁷¹ the results were stratified further. Of 268 operating room nurses questioned, 102 reported either urticaria, redness, or itching associated with latex glove use. Among the 197 who agreed to be skin tested with a latex extract, only 21 nurses, all of whom had symptoms, had positive test results. The highest percentage of positive test results (70%) was in atopic nurses with urticaria. Itching alone was least associated with a positive skin test result. Kelly et al.⁵⁴ examined 15 health care workers with latex allergy and 83 children with spina bifida. Eleven of the 15 health care workers had positive skin test results as did 42 of the 83 patients with spina bifida (some of whom had no clinical evidence of latex allergy). All patients who had experienced anaphylaxis had positive skin test results.

Epicutaneous testing has its risks, however. Kelly et al.⁵⁴ and others^{6, 60, 92} have reported anaphylactic events after epicutaneous skin testing. Although these cautionary reports form a distinctly small minority opinion among those investigators who have examined the use of skin tests, there is reason to be concerned. Anaphylactic events associated with skin testing have occurred without regard to risk group or history of anaphylaxis. There is at this time no FDA-approved skin test extract for rubber allergy. However, Bencard Allergy Laboratories (Mississauga, Ontario) and Stallergenes S.A. (Marseille, France) have latex extracts available for use outside the United States.^{57, 93}

The sensitivity and specificity of the *in vitro* measurement of latex-specific IgE is highly dependent on the population being studied. Patients with spina bifida typically have such high specific IgE titers that most *in vitro* assays are adequately sensitive.^{52, 54, 77} Our series at Children's National Medical Center has now reached a total of 93 patients with spina bifida evaluated with an ammoniated latex-based RAST. Thirty-five (38%)

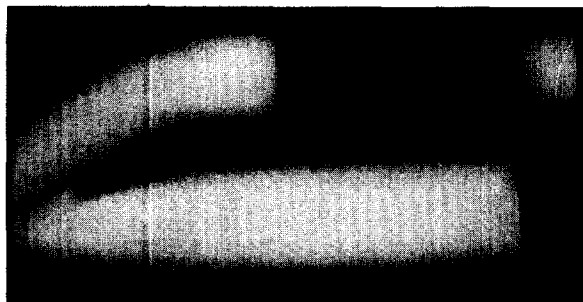


FIG. 1. The markings on a latex Foley catheter associated with an anaphylactic reaction in a patient known to be allergic to latex. The words *latex* and *rubber* do not appear anywhere on the catheter or its wrapper.

had positive RAST results; of the 58 patients with negative RAST results, only one reported a history consistent with rubber allergy. Thus the predictive value of a negative RAST result, even in this high risk group, is 98% (57 of 58). We have had no untoward reactions among any of the 57 patients with negative RAST results and negative history, even during latex-exposed surgery. These data suggest that the incidence of reactions in patients with spina bifida who have negative history and test results is extremely small.⁷⁷

In the past, in vitro diagnosis of latex allergy in health care workers and other adults with latex allergy has been considerably less sensitive.^{22, 52, 72} Pharmacia's latex RAST disc (Pharmacia, Uppsala, Sweden), the oldest commercially available product, has been associated with false-negative results in many studies of adults with latex allergy.* Although some of these patients with false-negative results may have had antigen-specific IgG₄,^{32, 94} recent technical improvements may have increased the sensitivity of in vitro testing for latex allergy. Hamilton et al.¹⁹ have reported that 82% of health care workers with respiratory symptoms caused by latex exposure have detectable specific IgE when the latex antigens are derived from Baxter Triflex gloves (Baxter Healthcare Corp., Hospital Supply, McGaw Park, Ill.). Halsey et al.⁹⁵ reported 91% to 100% sensitivity with a battery of antigens from ammoniated latex, nonammoniated latex, and glove extract, but the specificity was only 63%. McCullough and Ownby, using a biotin-avidin-amplified assay with liquid phase antigen, achieved 96% sensitivity in a group of adults with systemic allergic reactions; in the same group, the Pharmacia RAST result was

positive in only 50%. The specificity was about 80%.⁹⁶ If these results are borne out in larger trials, then the in vitro diagnosis of IgE-mediated latex reactions may approach the accuracy, if not the speed, of skin tests.

PREVENTION

Avoidance of latex products is the only measure that can avert a serious allergic reaction to latex. Given the ubiquity of latex in household and medical devices, complete latex avoidance is a daunting and perhaps impossible task. In the FDA series, 79% of reported reactions to medical devices (excluding barium enema catheters, condoms, and diaphragms) were due to latex gloves or bladder catheters. However, reactions were also reported to adhesive tape (5%), piston syringes (0.6%), intravascular administration sets (1.3%), and numerous other devices.⁷

Latex avoidance practices vary from center to center. At a minimum, latex avoidance entails the stringent elimination of latex-containing gloves and bladder catheters from the immediate environment. Condom catheters and balloons also constitute a clear hazard in patient rooms and outpatient settings. Penrose drains, latex bandages, rubber dams, prophylaxis cups, and rubber anesthesia masks have also been directly associated with type I reactions. Adhesives have usually been associated only with local reactions, but prudence would suggest the use of alternative, nonlatex products.

Well-documented episodes of aerosol spread of latex antigen have raised levels of concern beyond the direct contact of the patient who is allergic to latex with an antigen-containing device. Care should be taken to avoid the presence of *any* latex implements near the patient, and all surgical or dental assistants, even those who do not anticipate direct contact with the patient, should wear nonlatex gloves. Powdered latex products are especially dangerous because of possible aerosolization of antigen. Some centers have set aside latex-free areas in surgical suites and dental clinics; others have found it sufficient to reserve the first morning time slot, when the latex aeroallergen level appears to be lowest for procedures on patients with latex allergy.

In one case report latex antigen on the skin and clothes of a physician was implicated in anaphylactic episodes in his wife; his wife had been a nurse and had a positive skin test response to latex. The episodes disappeared when the husband washed carefully and changed his clothes

*References 17, 21, 74, 78, 88, and 90.

TABLE I. A partial list of surgical (S) and examination (E) gloves that, according to the manufacturers, do not contain latex

Name	Material	Type	Producer
Dermaprene	Neoprene	S	Ansell, Inc. (Dothan, Ala.)
Elastyren	Styrene butadiene	S	Hermal Pharmaceutical Laboratories, Inc. (Delmar, N.Y.)
Flexam	Polyvinylchloride	E	Baxter (Chicago, Ill.)
Neolon	Neoprene	S	Becton-Dickinson (Rutherford, N.J.)
SensiCare	Polyvinylchloride	E	Becton-Dickinson (Rutherford, N.J.)
Tactylon	Styrene ethylene butylene	S/E	SmartPractice (Phoenix, Ariz.)
TruTouch	Polyvinylchloride	E	Becton-Dickinson
Vinylite	Polyvinylchloride	E	SmartPractice

after work.⁹⁷ Therefore health care providers who have been using powdered latex gloves while caring for another patient should scrub their hands, arms, and faces thoroughly and change outer garments before entering the treatment area of the patient with latex allergy.

Health care workers with latex allergy can usually stay at work by switching to use of nonlatex gloves and asking colleagues to use powder-free gloves; for some workers, more stringent measures may be required. Such workers should be warned that when they become patients, mucosal or parenteral exposure to latex may result in anaphylaxis, even if the reactions during occupational exposure have been relatively mild.

Otherwise unexplained anaphylaxis in patients with latex allergy has suggested the possibility, first raised by Silverman,⁹⁸ that antigens may be released from rubber medication stoppers and the injection ports of intravenous tubing. Kwittken et al.⁹⁹ have reported such reactions in four children. Although the timing of the reactions strongly suggested that the anaphylactic reactions were caused by the injections into latex ports, in other, similar case reports the causative factors are less clear.¹⁰⁰ Nonetheless, in some centers it has become the practice to eliminate multidose vials and remove latex injection ports from the operating theater when the patient is allergic to latex. It must be stressed that the careful challenge studies that have been performed with gloves and glove powder have not been performed with these devices, which have been implicated by inference alone. An attempt to extract measurable antigen from injection ports failed, and a similar attempt on a vial stopper succeeded only after 40 needle punctures.²⁹ Thus the presence and bioavailability of antigen in these sources has not been documented.

Latex avoidance is made even more challenging by inadequate and at times frankly deceptive produce labeling, which makes complete latex avoidance extremely difficult without careful research and environmental control (Fig. 1). A recent letter from the FDA Office of Compliance and Surveillance indicates that labeling of gloves for latex content will, in the near future, be required.¹⁰¹ Autoinjectable epinephrine should be prescribed in case of accidental exposure, and the patient should be counseled to maintain a supply of nonlatex gloves at home.

Premedication with corticosteroids, H₁ antagonists, ephedrine, and in some series, H₂ antagonists has been used to prevent or ameliorate anaphylactoid reactions to radiocontrast media. Because accidental latex exposure can occur even in the best of circumstances, some authors have recommended that this regimen be used before major surgical and dental procedures are performed on patients with latex allergy.^{56, 102} This regimen has not been shown to be effective in preventing antigen-induced anaphylaxis, and it is not surprising that failures have been reported.^{99, 100} Therefore premedication cannot be used as an alternative to careful antigen avoidance. Nonetheless, premedication may reduce the severity of an antigen-induced reaction and should be considered.

Latex condoms have been associated with local urticaria in both men and women³⁹ and with one life-threatening anaphylactic reaction in a woman.⁶⁴ Unfortunately, latex condoms are the only proven barrier to the sexual transmission of human immunodeficiency virus and other sexually transmitted disease agents. Condoms made of lamb cecum do not prevent virus transmission and cannot be recommended as a risk reduction measure. A polyurethane female condom has been

approved by the FDA and is available; another condom made of styrene butadiene block polymer is awaiting final approval. Both of these products have been shown to block viral penetration in laboratory testing,^{103, 104} but the clinical efficacy of these devices has not been ascertained.

Health care workers are often concerned about the barrier effectiveness of nonlatex gloves. Since 1991, the FDA has imposed identical quality control standards on all medical gloves regardless of manufacture material.¹⁰⁵ Furthermore, the barrier effectiveness of latex gloves is highly variable.^{106, 107} Regardless of the barrier materials used, health care personnel should be reminded of the primary importance of intact skin and frequent handwashing in the prevention of the transmission of viral disease.¹⁰⁸ Table I is a partial list of gloves that do not contain latex according to the manufacturers.

ANTIGEN REDUCTION

Latex medical devices need not contain protein antigens. The protein content of *Hevea* latex products can be reduced considerably by washing, heat treatment, chlorination, and enzyme digestion.^{24, 25, 30, 109} Siler and Cornish¹¹⁰ have shown that natural rubber derived from alternative species (*Ficus elastica* and *Parthenium argentatum*) contains very little protein compared with *Hevea* rubber, and no cross-reactivity when measured with mouse polyclonal antisera. These approaches will be costly, especially at the beginning, and the products will need to be proven nonantigenic by using human sera and in vivo testing.

RECOMMENDATIONS

Both the American Academy of Allergy and Immunology and the American College of Allergy and Immunology have issued recommendations for latex testing and avoidance^{111, 112}; other recommendations have appeared as well.^{93, 113} This is a selective summary of those suggestions.

1. Questions about latex allergy should become a routine part of the patient history for primary care physicians, surgeons, obstetricians, radiologists, anesthesiologists, allergists, and dermatologists.
2. Patients in high risk groups should be identified and offered diagnostic testing, especially before medical or dental procedures that will entail latex exposure.
3. Patients with spina bifida are at such high risk for latex allergy that they should avoid latex exposure entirely, from birth.

4. Patients who have experienced any type I reaction to latex should be counseled to avoid latex exposure, to wear a Medic Alert bracelet (Medic Alert Foundation International, Turlock, Calif.), and to carry a supply of nonlatex gloves and autoinjectable epinephrine.
5. Health care institutions should be prepared to care for patients with latex allergy. This includes the availability of nonlatex devices and latex-free areas, a mechanism for screening patients, and appropriate patient care protocols.
6. The FDA should establish labeling guidelines for latex-containing medical devices without delay; other governmental agencies should institute similar labeling practices for nonmedical devices. If, for any reasons, labeling cannot be instituted, then a central database of the latex content of products should be maintained for ready access by consumers, hospitals, and health care professionals.
7. Health care institutions should establish procedures to deal with employees who are allergic to latex and should make nonlatex gloves available for their use. The use of powder-free gloves and latex-free gloves should be encouraged to reduce aeroallergen levels and to decrease the likelihood of sensitization in health care workers and patients alike.

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