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The diagnosis of natural rubber latex allergy

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Natural rubber latex (hereafter referred as latex) allergy, an IgE-mediated hypersensitivity reaction to constituent proteins retained in finished latex products (e.g., surgical gloves), has recently been identified as an international public health problem.¹⁻⁶ Latex allergy has been prevalent in patients with spina bifida, health care workers exposed frequently to latex at work, atopic patients, individuals who require frequent surgery, and workers in the latex industry.⁷⁻⁹ However, a number of patients with severe reactions, including fatal anaphylaxis associated with latex, have not been included in these groups, suggesting that other groups of individuals are at high risk.³ A wide spectrum of clinical manifestations ranging from contact urticaria, rhinoconjunctivitis, and asthma to severe anaphylaxis including death, has been associated with latex hypersensitivity.¹⁻⁹ Direct mucosal contact, inhalation, and parenteral exposure to latex proteins may lead to life-threatening reactions. Cutaneous exposure usually causes local reactions limited to the

area of contact but may progress to systemic features.¹⁰⁻¹⁴

Because practicing allergists are encountering an increase in the number of individuals with suspected latex allergy in their daily practices, clinical criteria and safe testing methods for diagnosis require definition. We summarize recent developments from latex allergy studies and introduce guidelines, which may be useful in the diagnosis of latex allergy. Screening for latex allergy through a medical history should be done for all patients, additional studies should be performed when the history is suggestive of latex allergy.

**CLINICAL MANIFESTATIONS OF
LATEX ALLERGY**

Only a few reports concerning the epidemiology of latex allergy have been published. Pediatric patients with spina bifida have a risk of operating room anaphylaxis related to latex that is 500 times greater than that of the general population.¹⁵ Between 28% and 67% of patients with spina bifida have latex-specific IgE antibody, but not all have clinical manifestations of latex hypersensitivity. Unfortunately, the first recognized reaction to latex may be anaphylaxis during medical procedures in the operating room or elsewhere in the hospital. A history of atopic disease such as asthma, food allergy, and prior anaphylaxis and symptoms of urticaria related to latex contact (e.g., symptoms after blowing up toy balloons or contact with rubber toys) help to identify patients with spina bifida at highest risk of anaphylaxis.

Anaphylaxis is not limited to patients with spina

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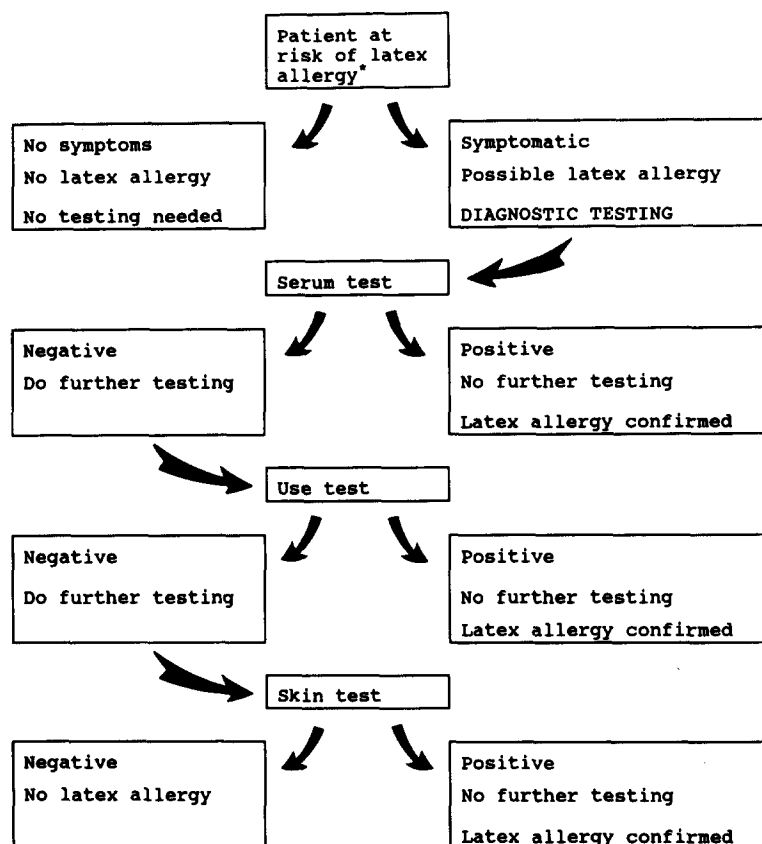


FIG. 1. Algorithm of diagnostic testing steps. *Note: Some investigators have advocated latex testing in all patients with spina bifida. This approach will identify patients who are free of symptoms but who have positive serum test results. Until further studies are performed, this select group should be considered allergic to latex.

bifida. Health care workers, patients with genitourinary tract anomalies requiring daily bladder catheterization, atopic patients, and patients with tropical fruit allergy have also had life-threatening anaphylactic reactions.^{16, 17} Their clinical histories, however, often vary from that of the patient with spina bifida. The majority of health care workers with symptoms of latex allergy, especially operating room nurses, physicians, dentists, and dental hygienists, are women and first have local hand symptoms when using latex gloves. These symptoms include immediate (<1 hour) pruritus, erythema, and urticaria; and episodes of recurrent irritant or contact dermatitis may precede these reactions. Although local urticaria is often induced by soluble latex proteins, serologic evidence of circulating latex-specific IgE may be absent, raising questions about nonprotein antigen involvement. Sensitive individuals may experience wheezing or flushing in the occupational setting, angioedema caused by contact of mucous membranes with latex products such as with con-

doms or dermatitis caused by household latex products, which may progress to anaphylaxis. Thus the clinical history is essential, and questions regarding latex hypersensitivity should be asked of all patients undergoing surgery or hospital procedures because these procedures may induce life-threatening allergic reactions. Although preoperative screening tests may be desirable, no sensitive, specific, safe, and rapid test exists in the United States at present.

Contact urticaria, pruritus, dermatitis, rhinoconjunctivitis, and asthma often herald the development of IgE-mediated latex hypersensitivity in health care providers. The incidence of latex hypersensitivity in this population ranges from 2.6% to 16.9% as reported in studies from Finland, France, and the United States.¹⁸⁻²⁰ Although limited numbers of patients are involved and sampling problems are inherent in such studies, they help to identify the magnitude of the problem. With over 5.5 million health care workers in the United States, an estimated 150,000 to 1

million may be sensitized to latex, placing them at risk for serious adverse reactions. Such reactions will result in significant economic loss in the form of workers' compensation and disability, as well as in medical costs encountered in caring for these patients. It is imperative that a medical definition of latex allergy be developed for the sensitized individual and for the insurance industry.

DIAGNOSTIC TESTING

An algorithm of diagnostic testing steps is presented in Fig. 1. A number of research laboratories have developed specific and sensitive *in vitro* serologic tests for latex-specific serum IgE by use of RAST, ELISA, basophil histamine release, flow cytometry, and immunoblots.^{5, 21-24} The accuracy of these tests varies because of differences in the latex source material used in latex exposure and because of potential cross-reacting antibody. The homology of epitopes in latex and food allergens resulting in cross-reactions may confuse the issue further. Latex contains at least 16 proteins of different molecular weights and likely contains closer to 240 different proteins (Viswanath Kurup PhD. Unpublished observation), all of which may be altered or partially degraded by the ammonia used in its preservation shortly after collection. Thus if the sensitizing latex product contains different epitopes than the material used in the assay a false negative test result may occur. Because of these inherent problems a sensitive and specific *in vitro* test has been generally unavailable to clinicians.

At present there is no latex skin test extract approved by the Food and Drug Administration. As a result, the clinician has resorted to skin testing with office extraction of available latex products such as surgical gloves. However, because of differences in latex supply sources and manufacturing processes, wide ranges of allergen content can be detected in various surgical gloves.²⁵ A standard testing method with minimal documented morbidity has been developed by a Finnish study group with the use of extracts of surgical gloves, whereas other investigators, using different extraction methods, have observed severe adverse reactions with skin prick testing.^{21, 26-27} The adverse reactions may be the result of variable sensitivities of the populations studied, a lack of standardization of major latex antigens, variation in skin test devices used, or use of highly potent antigenic extracts. Until a standardized safe extract is available, the clinician should rely on a medical history, physical examination, and

serologic tests carried out by reliable laboratories to confirm the diagnosis of latex allergy. Any skin prick tests with latex extract should be done in a hospital clinic with adequate resuscitation and medical support services available and an intravenous line in place or readily available for rapid administration of fluid and medications if necessary. The latex extract should be highly diluted (<1 ng/ml) for the initial test. The use of a single prick test may be safer than the MultiTest (Lincoln Diagnostics, Inc., Decatur, Ill.), which may approximate an intradermal test. Although the sensitivity of the prick test may be less than that of an intradermal test, the lack of antigen characterization precludes the use of the latter test except in a research protocol. These precautions should maximize the clinician's diagnostic capabilities and minimize the risk to the patient.

In the case of a negative serologic assay result and a compelling history, a "use test" may be done. A finger tip is cut from a latex surgical glove, dampened with water, and placed on one finger for 15 minutes after appropriate explanations of risk and benefit have been given to the patient. Urticaria with itching or erythema indicates a positive result. If no reaction ensues, placing an entire wet latex glove on the hand for 15 minutes or until a positive reaction occurs appears to be safe but will depend on the allergenicity of the glove proteins. A compelling history and a positive serologic test result eliminate the need for "use" skin testing.

In severe latex reactions in health care or industry workers for whom avoidance and medication fail to provide relief, workers' compensation or disability may be sought. The process and criteria used differ from state to state. Evidence of work-related illness, however, should follow standard clinical practice including a history, confirmatory immunologic studies, and measurements of disability such as pulmonary function.

SUMMARY

Allergy to latex is a rapidly emerging public health problem. Because our knowledge of the major allergens involved is incomplete, standardized *in vivo* and *in vitro* tests have not been available. Because of systemic reactions to skin prick testing, this method should be used only after results of other tests have been inconclusive. Risks and benefits of the test need to be explained to the patient, and until standard extracts of latex are available, skin tests should be performed under a research protocol. We anticipate that with

greater knowledge of the relevant allergens, purification of these allergens with affinity chromatography, high-performance liquid chromatography, and monoclonal antibodies, a safe and reliable extract will be available in the near future for skin testing. Until then, the above guidelines can serve clinicians in their daily practice in the diagnosis of latex allergy.

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