
Strategies for distinguishing asymptomatic latex sensitization from true occupational allergy or asthma

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Objective: To evaluate strategies for distinguishing those individuals with true occupational asthma caused by exposure to natural rubber latex from those individuals with allergic disease related to other allergens.

Data Sources: Article published between January 1, 1981, and December 31, 2001, were identified via a MEDLINE search with the following keywords: *latex, allergy, asthma, occupational asthma, and adverse reactions*.

Study Selection: English-language reports concerning diagnostic methods in latex and other forms of occupational asthma.

Results: Many methods have been evaluated for the diagnosis of latex allergy, including medical history, skin prick tests, in vitro tests, and various challenge tests. Skin prick tests with well characterized latex extracts are highly sensitive and specific predictors of latex-specific IgE antibodies; however, direct pulmonary challenge with latex allergen appears to be the only highly reliable method for diagnosis of latex-related occupational asthma.

Conclusions: It is difficult to optimally distinguish between occupational latex asthma and asymptomatic latex sensitization in a person with preexisting asthma using currently available techniques.

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INTRODUCTION

Latex is now recognized as a distinct occupational allergen capable of causing asthma and other forms of occupational allergic disease. One epidemiologic study¹ suggested that latex-induced occupational asthma affected 2.5% of 289 hospital employees and that some affected workers were not aware of their problem. This prevalence of disease is only slightly lower than a latex-related asthma prevalence of 9% observed in a plant making doll heads from natural rubber latex² and of 6% in a latex glove manufacturing plant.³ In a study of students studying dental hygiene technology, Archambault et al⁴ found that the incidence of occupational asthma was 4.5% during the 32 months of follow-up. This combination of a relatively high prevalence of asthma in occupationally exposed individuals, the potential short- and long-term morbidity of occupational asthma, and the large number of products manufactured from natural rubber latex makes it important for physicians, especially allergist-immunologists, to be able to recognize and accurately diagnosis latex-induced occupational asthma.

Discriminating between occupational allergic disease that results from exposure to natural rubber latex, occupational asthma due to other agents in a latex-exposed worker, and asymptomatic allergic sensitization to latex is fraught with many difficulties.^{5–7} In clinical practice, allergists typically rely on the patient's history to make a diagnosis of allergic disease. Sensitivity to allergens suggested by the patient's history is then confirmed by demonstrating the presence of

allergen-specific IgE with either in vivo or in vitro tests. A problem with these clinical criteria for diagnosis of allergic disease is how to resolve discrepancies between the patient's history and the results of tests for allergen-specific IgE when the diagnosis is likely to have a major impact on the life of the patient.

METHODS

MEDLINE searches for English-language articles published between January 1, 1981, and December 31, 2001, using the keywords *latex, allergy, asthma, occupational asthma, and adverse reaction* were conducted in an attempt to identify studies providing criteria for the diagnosis of latex allergy, occupational asthma, and, specifically, occupational asthma related to latex allergy. The primary purpose of this review was to find carefully validated methods for distinguishing asymptomatic allergic sensitization to latex from symptomatic sensitization.

RESULTS

All studies reviewed presumed that a careful history has been taken by a knowledgeable physician, but many questions are raised concerning the diagnostic validity of the clinical history of latex allergy. Many persons being evaluated for latex-related occupational asthma are health care workers. By nature of their medical knowledge, health care workers may consciously or unconsciously slant their history to more strongly suggest latex allergy. Previous medical knowledge and personal suspicion may also strongly influence how the worker perceives, interprets, and remembers events related to latex exposures. Workers concerned about latex allergy commonly obtain information from the Internet and from other

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health care workers, further influencing their history. Clinical history can also be complicated by reports of symptoms that resolved after self-medication.

While the clinician obtains the patient's clinical history, a number of relatively well established facts should be kept in mind.⁸ Allergic symptoms can result from either percutaneous or inhalation exposure to latex, but there must be a way in which the allergen can leave its source, be transmitted to the person, and then enter the person's body in a sufficiently large quantity to cause an allergic reaction.^{9,10} In some histories, the probability of sufficient allergen entering the body is remote. An example of this type of history was a patient who stated that she had an asthma attack after a person passed her in the hall carrying a sealed plastic bag of rubber bands. Under the circumstances described by the patient, it was difficult to hypothesize how sufficient latex allergen could have become airborne from the sealed bag of rubber bands.

Another common history concerns reactions following exposure to fresh latex paint. Although some brands of latex paints may contain small quantities of natural rubber latex, most latex paints used in homes and offices do not contain natural rubber latex. Even if the paint contains natural rubber latex, how can the latex allergens be transported from the paint to the person? If the person came into direct physical contact with the paint, such as while painting or from a splash or spill, then a reaction would be possible, but the airborne odor of latex paint is unlikely to carry significant quantities of allergenic latex proteins. Finally, the symptoms described by the patient should be typical of symptoms produced by other allergens, such as urticaria, asthma, rhinoconjunctivitis, or atopic dermatitis. Although other symptoms are certainly possible with latex and other allergens, it is harder to accept that only unusual symptoms are the result of exposure to latex.

As with other allergens, the value of the history increases if the symptoms are typical of allergic disorders, have an onset and course typical of allergic responses, always occur with latex exposure, and can be observed by other persons. If the person does not have any other allergic problems, the process is simplified. Latex-allergic individuals frequently are allergic to other allergens and have previously recognized allergic disease. Attempting to determine whether increasingly severe symptoms of asthma are related to the onset of latex allergy or the natural course of the disease can be difficult.

It is also important to document in detail the duration and extent of occupational exposure to latex both in the current job and in previous employment. Other exposures to latex, such as frequent dental or surgical procedures and latex condom use, should also be documented. Care must be taken in exploring the history of other allergic disease and possible reactions to the many foods known to cross-react with latex. Although none of these items will confirm a diagnosis of latex allergy, they can help substantiate enough exposure to latex to allow sensitivity to develop.

To evaluate the value of each method for diagnosing occupational latex allergy, it is useful to consider the comparison between the usual criteria for diagnosis vs the proposed absolute criteria presented in Table 1. Unfortunately, it is impossible to fulfill all of the absolute diagnostic criteria except in elaborate research settings. Beyond the history, the tools for evaluating possible occupational latex allergy are physical examination, skin tests, in vitro tests for specific IgE antibodies, pulmonary function tests, and allergen challenges.^{11,12} The physical examination is unlikely to provide findings supporting a diagnosis of latex allergy unless the worker is having acute symptoms following a recent latex exposure. This makes careful documentation of findings following acute exposures extremely important. In addition to vital signs, such as pulse, blood pressure, and respiratory rate, serial measurements of peak expiratory flow or spirometry may be helpful. Pictures of any rash or areas of edema may also be helpful.

Skin testing with licensed extracts of natural rubber latex has been shown to be a safe and reliable method for detecting latex-specific IgE antibodies in many European studies,¹³⁻¹⁵ but there is still no licensed commercial latex extract in the United States. The value of latex extracts made in the office is questionable, since there is no way to control for potentially large variations in potency and content of relevant allergens.

In vitro tests have been evaluated by many investigators for their ability to detect latex-specific IgE antibodies. Consistent with studies of many other allergens, in vitro tests for latex-specific IgE antibodies tend to be less sensitive and specific than skin tests.^{14,16,17} Table 2 lists the sensitivity and specificity of the assays for latex-specific IgE antibodies reported in several studies.¹⁸⁻²⁰ Although the results of these studies have varied, most demonstrate sensitivities of at least 70% with specificities of more than 90%. Some of the discrepancies between studies stem from differences in the standard used to define latex allergy. A frequent criticism of current in vitro tests is their ability to pick up antibodies apparently

Table 1. Criteria for Diagnosis of Allergic Disease

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| A. Clinical criteria for diagnosis of allergic disease |
| 1. A history of symptoms typical of allergic disease at a time and place when the person is likely to have been exposed to an allergen |
| 2. Demonstration of allergen-specific IgE to the allergen suggested by the history |
| B. Absolute criteria for diagnosis of allergic disease |
| 1. Induction of symptoms during a double-blind allergen challenge using an |
| a. appropriate dose of allergen |
| b. appropriate route of allergen exposure |
| 2. Placebo challenges under the same conditions must not induce symptoms |
| 3. Demonstration that the symptoms are the result of IgE-dependent mediator release |
| 4. The induction of symptoms must be reproducible |
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Table 2. Reported Performance of Assays for Latex-Specific IgE Antibodies

Study	No. of serum samples	Assay evaluated*	Standard used†	Sensitivity, %	Specificity, %
Niggeman et al ¹⁸	146	CAP	Clinical history	100	49
		Magic Lite	Clinical history	100	50
		EAST	Clinical history	100	49
Hamilton et al ¹⁹	312	CAP	SPT	76.3	96.7
		AlaSTAT	SPT	73.3	97.2
		HY-TEC	SPT	91.6	73.3
Ownby et al ²⁰	143	CAP	SPT and clinical history	79.5	90.2
		AlaSTAT		73.8	91.7
Gruber et al ¹⁷	108	CAP	Latex glove challenge	94	76
		AlaSTAT		74	88

Abbreviation: SPT, skin prick test.

* Assays evaluated include AlaSTAT (Diagnostic Products Corp, Los Angeles, CA), CAP (Pharmacia-Upjohn, Kalamazoo, MI), HY-TEC (Hycor Biomedical, Garden Grove, CA), Magic Lite (ALK, Copenhagen, Denmark), and EAST (Allergopharma, Reinbek, Germany).

† Standard used to determine true latex sensitivity.

induced by other allergens that happen to cross-react with latex allergens.^{21–25} If the manufacturer tries to reduce interference by cross-reactive IgE antibodies by raising the decision point of the assay or by removing some individual proteins, an increasing percentage of truly positive serum samples will be incorrectly classified as being negative, thereby reducing sensitivity. A hope for the future is that using combinations of specific, pure latex allergens will increase assay sensitivity and specificity.²⁶ However, even with highly sensitive and specific tests, physicians must constantly remember that a positive test result establishes only the presence of allergic sensitivity (IgE antibodies) not the presence of allergic disease.^{27,28}

Other widely accepted tools for the evaluation of occupational asthma are evaluation of bronchial hyperresponsiveness to agents, such as histamine or methacholine, and workplace spirometry.^{1,3,5,11,29} Some authorities feel that occupational asthma cannot be present if bronchial hyperresponsiveness is not also present, provided the person is still working in the same environment.⁵ If the person has been away from the environment, bronchial hyperresponsiveness may be reduced or absent.⁵ To be fully acceptable, workplace spirometry must be performed by a well qualified and impartial person. These simple requirements often make it difficult to obtain valid spirometry results. As with bronchial hyperresponsiveness, workplace spirometry requires that the person still be working in the same environment. It also requires that the person step away from work to perform spirometry and that a qualified but impartial person be available to perform the testing at the work site during the person's normal work shift. Unfortunately, there are no widely accepted equivalent tests for other allergic problems, such as rhinitis, sinusitis, and atopic dermatitis.

The current standard for latex-related occupational asthma is spirometry before, during, and after a simulated latex exposure.^{5,30} Bronchial hyperresponsiveness may also be evaluated before and after challenge. Several small studies^{31,32} have shown that challenges with airborne latex have

produced symptoms in persons thought to have latex-induced asthma. Kurtz et al³³ performed inhalation challenges in a hooded exposure chamber with latex allergen-coated cornstarch particles in 26 individuals (23 with latex allergy and 3 atopic control subjects). Twenty-two of the 23 individuals with latex allergy responded to the challenge, whereas none of the control individuals responded. Kurtz et al³⁴ subsequently reported that this challenge method was reproducible and that repeated challenges did not appear to increase latex sensitivity.

The largest study to date was conducted by Vandenplas and colleagues,³⁰ who evaluated 45 individuals consecutively referred for evaluation of possible latex-related asthma. A standardized clinical history was obtained from each patient and reviewed by four expert physicians. Skin prick tests were performed with two different commercial latex extracts along with spirometry and histamine challenge. The standard for diagnosis of latex-related occupational asthma was a positive response to an inhalation challenge with powdered latex gloves. Thirty-one (69%) of the 45 study subjects responded to the inhalation challenge. Agreement among the four physicians who reviewed the histories concerning the presence of latex-related asthma was poor, and the consensus decision was a poor predictor of the results of latex challenge. The sensitivity of the consensus history was good at 87%, but the specificity was poor at 14%, giving a positive predictive value of 75% and a negative predictive value of only 50%. Similarly, the bronchial challenge with histamine had a good sensitivity of 90% but a specificity of only 7%. The results of skin tests were slightly better, with a sensitivity of 100% but a specificity of only 21%. The combination of history and skin test provided a sensitivity of 94%, a specificity of 36%, a positive predictive value of 76%, and a negative predictive value of 71%. The major conclusion from these results is that the best way to detect latex-related asthma is to challenge the person with latex. This conclusion is consistent with a num-

ber of other studies that have reported various methods for performing latex inhalation challenges.^{1,31,33}

The major problem preventing acceptance of bronchial challenge with latex as a diagnostic standard is the lack of a widely accepted, standardized challenge method that has been well characterized in terms of reproducibility and safety. Challenge methods also require a well characterized source of latex allergen. A final limitation of bronchial challenge is that it has been shown to be useful only for asthma and not for other forms of allergic disease. The possibility of adverse reactions from the challenge is a significant concern. Although no severe reactions have been reported following inhalation challenges with latex, some case reports suggest that inhalation exposure can lead to anaphylactic reactions.³⁵

Because of concerns about the safety of latex inhalation challenges, other forms of challenge have been evaluated for documenting latex allergy. If these challenge procedures could be validated, they could also allow the investigation of other forms of latex-related occupational disease. Palczynski et al³⁶ evaluated nasal challenges with latex extracts in latex-sensitive nurses, atopic nurses who were not latex sensitive, atopic patients not regularly exposed to latex, and healthy, nonatopic controls. These investigators chose to use a single 5-minute challenge with 6 mL of latex extract at a concentration of 1000 µg/mL of natural rubber latex protein. The subjects were examined at 0.5, 4, and 24 hours after the challenge for nasal symptoms, nasal eosinophils, and nasal basophils. The parameter that best distinguished the latex-sensitive nurses from the other groups was the number of nasal eosinophils at either 4 or 24 hours. Challenges performed by having subjects don either part or an entire latex glove have been proposed by numerous investigators, but the true sensitivity and specificity of this type of challenge have not been well documented. A major problem with this form of challenge is the requirement of an adequate supply of fresh, high-allergen-content latex gloves to use in the challenge. Since most manufacturers have made many changes to try to lower the allergen content of their gloves, securing high-allergen gloves can be difficult.

CONCLUSION

Carefully distinguishing between asymptomatic latex sensitization and latex-induced occupational asthma is difficult. Much of this difficulty comes from the lack of well characterized latex extracts and well characterized methods for safely challenging patients to demonstrate the causal link between latex exposure and disease symptoms.

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