

Position statement

The use of in vitro tests for IgE antibody in the specific diagnosis of IgE-mediated disorders and in the formulation of allergen immunotherapy

This position statement has been approved by the Executive Committee of the American Academy of Allergy and Immunology and is based on the latest objective information available. It will continue to be reviewed for accuracy and timeliness. If new data become available, the statement will be modified, as required.

Preamble

This position statement revises and extends a previous statement prepared by the Academy's Practice Standards Committee and approved by the Executive Committee in March 1983.¹ Much of the previous statement is still sound and will not be reiterated here. Specifically, sections dealing with the proper management of allergic patients and the requirements for physicians who wish to evaluate and treat allergic patients remain valid and worthy of review. Revision and refinement of the original statement is needed at this time, however, to reflect a number of interval changes. These changes include the proliferation of in vitro allergy tests during the last 5 years, the increasing use of these tests by physicians newly drawn to the practice of allergy, and changing attitudes and data regarding the relative merits of in vivo versus in vitro allergy testing, including relative cost-effectiveness. The present statement responds to these and other events and points to some needed additional research and changes in policy.

Background

Historical background. The prototype for in vitro analysis of IgE antibody in serum was the RAST, initially described by Wide et al. in 1967.² This test was first made commercially available by Pharmacia Laboratories (Uppsala, Sweden) and later copied by other laboratories. By the early 1980s, the market for

Abbreviation used

FDA: Food and Drug Administration

in vitro allergy testing had grown sufficiently to attract other companies to develop alternative solid-phase immunoassays that involve newer technologies. These "RAST analogues" have used different solid phases to fix the allergens, a variety of tracers attached to the IgE-detection protein, and alternative instruments to read out the final signal.³⁻⁶ Several novel "second generation" technologies for in vitro allergy testing are poised for introduction. Improvement in the facility of in vitro testing has made possible the adoption of these techniques in physicians' offices in which they now may be used as an alternative to traditional allergy diagnosis by skin testing. This possibility has encouraged physicians other than allergists to undertake allergy diagnosis and treatment in their patient populations. Within the last few years, several screening tests for allergy have been licensed. Their approach has not been uniform but, in general, these tests purport to provide qualitative information on the presence or absence of serum IgE antibodies for a battery of the most prevalent allergic sensitivities. These devices are being marketed largely to primary care physicians who can now "screen" for allergic disease at a reasonable cost. These innovations in the last 5 years are reshaping the practice of allergy in the United States and deserve careful analysis.

Technological approaches. The several available methods for the measurement of IgE antibody in serum involve a variety of technologies. They can, and often do, provide discordant results. These results can be explained, in part, by differences among the allergen extracts used in each assay, the variability with which each technique insolubilizes all of the relevant allergenic molecules in a mixture, the recommended incubation times, the anti-IgE antibody used in each assay, and the threshold criterion recommended by each manufacturer. Even though these newer systems

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are licensed for clinical use, their relative performance is largely unevaluated, especially for less common allergens. In different test systems, there is no consistent correspondence between arbitrary class scores and ranges of IgE antibody. Furthermore, the threshold criteria for positivity often vary among technologies, and even between competing scoring schemes used with the same technology. A myriad of classification schemes have emerged for reporting test results, leading to further confusion among physicians who use different vendors or clinical laboratories. A task force report on in vitro diagnostic tests concluded, "Currently, in vitro IgE tests from different commercial sources are virtually impossible to compare—a state of affairs almost unprecedented in modern laboratory medicine."⁷

Quality control. Since the 1983 Academy position statement, regulatory oversight has been increased at the federal level, leading to a decline in the number of obviously invalid tests being offered in kit form or in commercial laboratories. Although commercial laboratories are mandated to participate in quality control programs, none was available for IgE antibody testing until 1985 when an allergy diagnostic panel was first offered by the College of American Pathologists. This program has not yet satisfied the requirement for quality control exercises, especially in physicians' offices in which in vitro tests are sometimes performed by inexperienced personnel with minimal oversight. The problem is complicated by the fact that each technology offers not a single test, but a battery of 50 or more tests, each of which requires its own quality control program. Thus, in 1992, physicians cannot be assured that the results that they obtain from in vitro allergy tests are generally valid and reproducible.

Clinical interpretation of results. The clinical interpretation of in vitro tests for IgE antibody is plagued by the same difficulties as interpretation of traditional allergy skin testing. During the last 5 years, little additional information about the diagnostic accuracy of individual IgE antibody tests has been acquired, whether performed in vivo or in vitro, in predicting clinical sensitivity to specific allergens in well-defined allergic diseases. Diagnostic tests for food allergy are particularly a problem in this regard. The quantitative potential of in vitro allergy testing allows for the possibility of increased diagnostic accuracy, but this potential has failed to materialize.

Relative merits of skin tests versus in vitro measurements of IgE antibody

Technical performance. In the hands of experienced physicians, skin testing by either puncture or intra-

dermal methods continues to provide acceptable diagnostic information at negligible risk to the patient. The results are available immediately. This permits prompt integration of the information obtained into the patient's differential diagnosis. A positive skin test is dependent on not only IgE antibody but also mast cell integrity and vascular and neural responsiveness. In practice, however, the latter two factors are not highly intrinsically variable, and the skin test is believed to reflect largely the presence of specific IgE antibody. Under ideal conditions, prick/puncture (epicutaneous) testing provides results that are highly concordant with optimized in vitro tests for IgE antibody.⁸⁻¹⁰ Additional sensitivity can be achieved by intradermal testing that is clearly indicated for the diagnosis of anaphylactic sensitivities to stinging insects and to drugs.^{11, 12} Puncture skin testing and in vitro tests for IgE antibody both appear to be of sufficient sensitivity to detect most cases of aeroallergen disease.¹³⁻¹⁷ However, some studies suggest that more sensitive intradermal tests are required to confirm the diagnosis of allergic disease in some less sensitive patients.⁹ Reproducibility of skin test results among experienced physicians is likely to be very good if both use standardized extracts of known potency.¹⁸

In contrast, in vitro tests for IgE antibody offer a number of potential advantages not readily available for skin tests. Solid-phase immunoassay reagents have long shelf lives and are amenable to ongoing quality control for stability and reproducibility that is not easily accomplished in an office with skin tests. It should be possible to define precisely the performance parameters (sensitivity and variability) for each in vitro IgE test, although this information is not currently available to most users. The results of in vitro tests are not influenced by pharmacotherapy, and thus, medications do not have to be withdrawn before testing. The small but finite risk of systemic reactions to skin tests can also be avoided. Results from properly standardized in vitro tests or IgE should be reproducible among laboratories as well as among test methods. Results from available proficiency surveys, however, suggest that, whereas there is good qualitative concordance for strongly positive sera, the results with weakly positive sera or negative sera are much more variable between laboratories and among methods.^{5, 19-22} This appears to be due, at least in part, to differing threshold criteria, but differential test sensitivity probably also plays a role.

Diagnostic accuracy. Both skin testing and in vitro IgE tests have sufficient sensitivity and specificity to confirm the diagnosis of most cases of inhalant allergy. The extra sensitivity afforded by intradermal skin test-

ing is important for maximizing the negative predictive value in testing for anaphylactic states^{11, 23} and is useful in establishing an allergic origin for respiratory symptoms in less sensitive individuals⁹ or when allergenic extracts are of suboptimal potency. There is, however, a paucity of data relating clinical risk and/or symptoms to results of in vitro diagnostic tests.

Economy. Although no systematic appraisal has been done, national insurance reimbursement data indicate that in vitro IgE testing is currently at least twice as costly per test as skin testing.* In vitro tests enjoy the potential of savings by economy of scale and technologic advances that can be expected to increase test efficiency. However, although the cost of in vitro IgE tests has decreased as much as 50% in the last decade, diagnosis by skin testing remains favored on economic grounds at the present time.

Abuse potential. Both skin testing and in vitro allergy tests are open to abusive practices. Overuse of testing, both in the number of patients tested and the number of allergens tested for, is the most common source of abuse. Increased federal regulation has significantly reduced the number of invalid allergenic extracts and in vitro tests available in recent years, and this trend is to be encouraged. On a national scale, the abusive potential of in vitro tests is far greater because of universal access, especially to physicians who have little experience or training in allergic diseases. The most costly abuse may be unwarranted immunotherapy prescriptions for individuals with weakly positive in vitro test results but no other clinical evidence of allergic disease. Other abuses include frequent monitoring of response to immunotherapy.

Recommendations regarding the proper use of in vitro tests

For diagnosis of individual allergic patients. In the hands of an experienced and well-trained physician, in vitro tests for IgE antibody, although they are currently more expensive than skin tests, can be used as an aid in accurate diagnosis of most cases of inhalant allergies and IgE-dependent food allergy. For accurate clinical diagnosis, results of in vitro testing, as for skin testing, must be integrated with a pertinent and thoughtful clinical evaluation. In vitro tests cannot, at the present time, be recommended for the definitive diagnosis of anaphylactic sensitivities to stinging insects and drugs. If these tests are positive, such in vitro tests are likely to be confirmed by intradermal skin tests, but negative in vitro tests for drugs and

stinging insects have been observed in high-risk patients with positive skin tests.^{11, 12}

For screening for allergic diseases. Multiple-allergen in vitro tests may be a cost-effective means of confirming a clinical suspicion of IgE-mediated symptoms based on careful history and a physical examination. For the allergy specialist, such tests are more likely to be useful in confirming the absence of significant IgE specificities in patients believed, on clinical grounds, to have nonallergic respiratory disease. Because IgE immune responses occur more frequently than symptomatic disease, there is an appreciable risk of over diagnosis if such IgE screening tests are applied indiscriminately to unscreened or self-screened populations.²⁴ It has yet to be established that such allergy screening tests are cost-effective when used by primary care physicians. Furthermore, the clinical value of these tests in the evaluation of young children in which IgE antibodies may precede allergic symptoms has not been adequately assessed. Restraint and further research can be recommended at this time.

For formulation of allergen immunotherapy. Validated in vitro IgE tests can be usefully used to design safe and effective immunotherapy for patients with inhalant respiratory allergy.²⁵ Once again, intelligent use of in vitro data for this purpose requires consideration of clinical factors that must be integrated into the final decision by a knowledgeable physician who has observed and evaluated the patient. It is inappropriate and potentially dangerous for physicians or testing laboratories to apply formulae for immunotherapy prescriptions based only on the results of in vitro IgE tests. It is an alarming trend that such practices continue to increase in prevalence, since they clearly do not serve the patient's best interests. The Academy has already expressed its concern about this "remote practice" of allergy in a position statement.²⁶

Recommendations for future research and policy endorsements: Efforts at improved standardization and performance

Manufacturers' responsibility. Manufacturers of in vitro IgE tests have the ethical and legal responsibility to assure the quality of their products. Receiving a license from the FDA (especially via the shortcut of demonstrating equivalency to RAST) is necessary but not sufficient to meet this responsibility. As recommended by a recent Task Force,⁷ manufacturers should provide the end user with additional information on reagents used in the assay system, especially the source and quality of the allergenic extracts used. Data on stability and lot-to-lot consistency should be published for each individual assay offered. The perfor-

*Data from Aetna insurance, kindly provided by Henry M. Williams, Director of Medical Policy.

mance parameters of each assay (sensitivity, specificity, precision, and reproducibility) should be made readily available, preferably in the package insert, for each test offered with standard guidelines currently under development by the Academy's Committee on In Vitro Tests. Finally, manufacturers should strive to establish the clinical diagnostic accuracy of their tests by sponsoring controlled studies to determine the predictive value of results for the presence of symptomatic allergy as well as the intensity of symptoms in well-defined clinical allergic states.

Regulatory responsibilities. Federal authorities (the Centers for Disease Control for clinical laboratories and the FDA for test-kit licensure) should exercise their regulatory responsibilities to assure the validity and quality of in vitro tests for IgE antibody. This can be greatly facilitated by mandating the participation of clinical laboratories and physicians' offices in proficiency testing programs (see below) and by requiring manufacturers to provide more data on extracts and on single test performance to practicing physicians. It is also recommended that each allergen test be licensed separately with a requirement for demonstrated validity for each specific test, rather than only for the method as a whole. An allergy-test advisory committee may be useful in assisting the Division of Medical Devices of the FDA in its formulation of policy in this area.

Proficiency testing programs. The quality control of individual laboratory results, as well as useful comparison of various test methodologies, is most efficiently accomplished by widely subscribed proficiency testing programs. The Academy endorses the IgE-antibody testing program, offered by the College of American Pathologists, and encourages participation by all laboratories and physicians' offices performing IgE in vitro tests. In addition, manufacturers should endorse this program to their clients and consider subsidizing their participation in it since they also have much to gain from this program.

Endorsement of quantitative approaches

The arbitrary reference systems with myriad class-scoring schemes should be abandoned in favor of quantitative reporting methods in which test results are reported in units that are proportional to antibody content. Quantitative reporting offers numerous benefits, including facilitation of the usual statistical criteria for threshold selection and determination of precision profiles. Furthermore, quantitation is a necessary prerequisite to defining more precisely the diagnostic accuracy of IgE in vitro tests and the relationship between quantity of IgE antibody and the symptoms or risks of disease.

Clinical research to establish the predictive accuracy of IgE-antibody levels in IgE-mediated disorders

More clinical research is much needed to provide information about the diagnostic accuracy of individual IgE antibody tests, whether performed in vitro or in vivo, and their use in predicting clinical sensitivity in well-defined allergic diseases.

Cost-effectiveness studies

The issue of the relative cost-effectiveness of skin testing and in vitro IgE tests needs to be addressed definitively. Third-party insurers should make available their data on charges and reimbursement for alternative methods of IgE testing. Furthermore, because of the use of mixtures with skin testing and multiallergen in vitro tests, the aggregate cost of an average allergy evaluation by the two diagnostic methods also needs to be determined more precisely. Finally, a careful analysis of the cost-effectiveness of the use of allergy screening tests by primary care physicians as a basis for allergy referral or in large-scale screening of unselected populations needs to be undertaken before the appropriate role of these tests can be defined.

CONCLUDING SUMMARY

In principle, in vitro tests for IgE constitute a technically valid method for detection of allergen-specific IgE antibody in serum. When these tests are performed and appropriately interpreted in the light of clinical history and physical examination, obtained personally by a physician properly trained in the diagnosis and treatment of allergic and immunologic diseases, in vitro tests for IgE can provide a satisfactory alternative to skin testing for confirmation of the diagnosis of most patients with clinically significant aeroallergen disease and IgE-dependent food allergy.

In vitro tests for IgE are comparable in sensitivity to prick/puncture skin tests. Intradermal skin testing is more sensitive and is required for the definitive evaluation of insect-sting allergy and drug allergy and, in some cases, of aeroallergen disease in which either patients are minimally sensitive or available extracts are of suboptimal potency for skin testing.

Currently, skin testing is more economical per test than in vitro IgE tests, and therefore, properly performed skin testing is the test of choice. Selective use of in vitro tests can be justified in patients with extensive dermatitis or dermographism, in patients who cannot be withdrawn from medications that interfere with proper skin testing, and occasionally, in patients who otherwise refuse skin testing.²⁷

The abuse potential for in vitro tests in aggregate exceeds that of skin testing because of universal availability of the former. Abuses of particular concern include the screening of unselected populations and the use of in vitro test results for translation into immunotherapy prescriptions without an appropriate clinical evaluation, the so-called "remote practice of allergy."

The American Academy of Allergy and Immunology endorses efforts both by manufacturers and responsible regulatory agencies to improve standardization and performance of in vitro tests for IgE. Widely subscribed proficiency testing programs are essential for local quality control and continual test improvement. Quantitative reporting of results of in vitro tests will facilitate better definition of the relationship between quantity of IgE antibody and the symptoms or risks of disease. Finally, additional research is needed to provide data on the predictive accuracy of IgE antibody levels in a variety of IgE-mediated disorders and to establish the relative cost-effectiveness of skin testing and in vitro tests in a comprehensive and meaningful manner.

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