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## CME Review article

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# Usefulness of specific IgE antibody tests: a progress report

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**Learning Objectives:** To enable the readers to recognize some of the history, problems, progress, interpretation, and present status of assays for specific IgE (s-IgE) antibodies.

**Data Sources:** Peer-reviewed literature in the field.

**Study Selection:** Key articles were selected by the author.

**Results:** Clinical and analytical studies have differed widely in their conclusions as to the performance of tests for s-IgE. Study conclusions depend on the testing method used, the allergen(s) studied, patient selection, and, most importantly, the standards used for comparison. Today, only a handful of the once commercially developed assays still exist, and some of these still do not compare well to an analytical ideal standard. However, with the extent of regulation and economic pressures, most of the surviving s-IgE tests are considerably improved over what had existed before them.

**Conclusions:** Allergic diseases with multiple symptom patterns seem to be increasing in modern societies. Objective methods are needed to differentiate allergic origins from other mechanisms that cause similar symptoms. Accurate, quantitative, and objective methods for s-IgE measurement are now available and can be used effectively in clarifying allergic diagnoses when interpreted in conjunction with the clinical history.

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## INTRODUCTION

Large numbers of anecdotal reports in the medical literature indicate that specific factors in the serum are largely responsible for allergic symptoms. This article aims to enable readers to recognize some of the history, problems, progress, interpretation, and present status of assays for specific IgE (s-IgE) antibodies. Key articles were selected from the peer-reviewed literature in the field. This article includes a short history of how and why s-IgE assays were developed, the origin and explanation of several controversies in this field, and where these tests stand today. In addition, a review and update of test result interpretation with an emphasis of the advantages of treating patients with allergic disease using quantitative s-IgE tests are included.

## HISTORY

History records a number of anecdotal reports that have reinforced the idea that specific factors in the serum are largely responsible for allergic symptoms, such as hay fever, asthma, and anaphylaxis. The classic Prausnitz-Kustner experiment (P-K reaction) and a series of follow-up experiments by De Besche in 1921 provided the first unequivocal

proof of this.<sup>1,2</sup> The exact nature of this serum factor was elusive until the middle 1960s. At that time, a variety of studies had shown that the postulated “atopic reagin” exhibited immunologic specificity, but its activity was not found in the known immunoglobulin classes IgG, IgA, IgM, or IgD.<sup>3</sup> In 1966, using immunochemical observations, Ishizakas et al<sup>4,5</sup> demonstrated that the factor responsible for skin whealing and erythema reactions to ragweed allergen extract was a unique immunoglobulin class present in the serum in low concentrations. They named this *gamma E globulin* because of its association with erythema. Independently, Johansson and Bennich<sup>6</sup> from Sweden discovered an atypical myeloma that produced a unique immunoglobulin called *IgND*. Small amounts of this protein were capable of blocking the P-K reaction.<sup>7</sup> Subsequent studies demonstrated that both groups had been working with the same substance. After reviewing these data, the World Health Organization deemed the existence of a new immunoglobulin class (IgE) in 1968.<sup>8</sup>

Having the myeloma, it was a natural step to make specific antibodies to this protein and construct assays to examine its presence in various serum samples. The principles for radioimmunoassay as set out by Nobel Prize winners Yalow and Berson<sup>9</sup> were used for this purpose. Shortly thereafter, assays for total serum IgE (paper radioimmunosorbent test) were available, and elevated levels demonstrated a strong but imperfect relationship to clinical allergy.<sup>10,11</sup> To evaluate the specificity of this IgE, the total IgE assay was modified by

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attaching proteins from different allergen extracts to a cellulose solid phase, incubating these with serum samples, and measuring the s-IgE antibodies bound with isotopically labeled antibodies specific for IgE.<sup>12</sup> The relative amount of s-IgE to a given allergen preparation was related to that from a pool of birch-sensitized individuals measured in similar fashion. This test was commercialized by Pharmacia (Uppsala, Sweden) in 1974 and was named the radioallergosorbent test or Phadebas RAST.<sup>13</sup>

With a new objective test for allergic disease, enthusiasm for s-IgE testing grew, and new allergens were added to the repertoire of tests being offered. As s-IgE testing grew in popularity, a number of commercial companies and private laboratories introduced new and different test formats for the measurement of s-IgE. These were essentially variations on the same immunoassay theme, using different protocols, solid phases, coupling chemistries, allergen preparations, detection antibodies, and standards. Many of these were generated with the idea of providing automation for large laboratories. By the end of the 1980s, more than a dozen different commercial varieties of s-IgE tests existed.

During this time, a group of physicians who used titrated intracutaneous skin tests for allergy diagnosis believed that the Phadebas RAST s-IgE assay lacked sensitivity. Several changes were suggested, which included longer incubation times, normalization for radioactive decay, lowering the cut-off between positive and negative, and comparison of the s-IgE results to a single point total IgE standard. This resulted in the so-called modified RAST introduced and popularized in 1978 by Nalebuff et al.<sup>14</sup> This simplified format indeed increased the sensitivity of the test (by lowering the cutoff) and facilitated reporting results but was accompanied by a number of other drawbacks as pointed out in several studies. These included poor precision at the low end,<sup>15</sup> the likelihood of increased false-positive results,<sup>16–18</sup> concerns about quantitation,<sup>19</sup> poor performance with some allergens,<sup>15</sup> and discrepant results by different manufacturers.<sup>15</sup> Later studies questioning the value of the intracutaneous skin test have indicated that this procedure may be an inadequate standard on which to base an assay cutoff.<sup>20–22</sup>

Analytical studies pointing out discrepant results among several of these different s-IgE assay methods collectively began to raise skepticism regarding their performances.<sup>23–25</sup> Adding to the controversies were variable results when comparing s-IgE test results to different clinical standards.<sup>25–29</sup> This confusion was not helped by the fact that the results from all the different test methods were reported as seemingly identical class scores (invented to make results easier to use for physicians). This problem created the impression that results from the different assays were indeed equivalent or interchangeable, a fact disputed by a number of different studies.<sup>15,30,31</sup> Unfortunately, the trademark RAST became used colloquially (and still is) to refer to all s-IgE measurements regardless of the technology used. This served to

further obscure the fact that these were different assays with different analytical and clinical performances.

In 1992, Pharmacia introduced a new system for measuring s-IgE.<sup>32</sup> This system provided a large solid-phase surface area for binding allergenic proteins, well-qualified allergen extracts for coupling, a mixture of monoclonal and polyclonal anti-IgE antibodies to enhance assay range, and automation to reduce errors and increase throughput.<sup>33</sup> In addition, this assay was linked to the World Health Organization standard 75/502 for IgE using a 6-point calibration curve. A not well-appreciated fact was that Pharmacia replaced their own test, the Phadebas RAST, which was the market leader at this time with this new test called the Pharmacia CAP System. A considerable number of studies performed worldwide have confirmed that this system yields essentially quantitative measurements of s-IgE to a large number of different allergens with accuracy and precision and is considered the present reference standard for these measurements in the world today.<sup>30,33–37</sup>

## IMMUNOASSAY CONSIDERATIONS

Many of the problems with these assays in the past and a number of the improvements introduced are best understood by consideration of simple immunoassay principles. The s-IgE assays are multicomponent assays that involve the measurement of different IgE antibodies with different affinities to different allergens. Since allergic individuals can be sensitized to any or all of the proteins from a given source, their accurate evaluation requires that all relevant allergens be present in a recognizable manner on the solid phase. This is usually demonstrated by immunoblotting a large number of serum samples from specifically sensitized individuals and showing that s-IgE to these different specificities are removed by a particular solid phase.<sup>34</sup> This is in fact how major and minor allergens from different sources have been defined. During development of the early s-IgE assays, little information was available regarding these allergens and their coupling efficiencies. In addition, many of the early assays used commercial allergen extracts from different sources (same as those used for skin testing). Since many of these were poorly characterized and of questionable potency, a significant source of variability for and among the different assay formats became understandable.

Immunoassays typically measure tens to hundreds of billions of molecules (1 ng of IgE is approximately 30 billion molecules) and thus operate under the providence of the laws of mass action. These laws dictate that immunoassays depend on association ( $K_a$ ) and dissociation ( $K_d$ ) rates that at equilibrium are measurements of affinity. An absolute requirement for an assay to be quantitative states that the concentration of the binding sites (allergen) of interest must be present in excess.<sup>38</sup> In fact, whenever the product of the  $K_a$  times the number of binding sites is greater than 10, an assay

will be essentially quantitative.<sup>38</sup> Since s-IgE assays are multicomponent systems and many of the allergens from a given source are not known, the only feasible solution is to have a large excess of all possible antibody-binding sites. An assay not satisfying this requirement becomes affinity dependent and only measures a fraction of the antibodies present regardless of their concentration. It is clear that in the past this has been the case for most s-IgE assay methods.<sup>15,17,30</sup> This has been well demonstrated by experiments with paper disk-based systems where, following incubation with a given serum sample, the remaining serum gives repeatedly the same result for several rounds until the antibodies begin to be depleted.<sup>39</sup>

Immunochemical principles also dictate that for an assay to be quantitative it must exhibit log-log dilution curves over its reporting range that are parallel to those of the standard.<sup>40</sup> Studies on the modified RAST and other early tests with several allergens demonstrated clearly that this was not the case and provided additional information that these types of assays were most likely affinity dependent and as such are unlikely to give quantitative information.<sup>17</sup>

Another important immunochemical concept for consideration is that of cutoffs. For example, at what point is an assay to be considered positive and when is it negative? This can be determined analytically using statistics where 3.3 SDs from the mean of negative measurements result in a 5% overlap of false-negative and false-positive results.<sup>41</sup> This also assumes that the distribution of the low-level positive results is similar to that of the negative results, which is unlikely. Thus, arbitrary cutoffs for these assays have usually been made several SDs above 3.3 in consideration of this possible problem.<sup>18</sup> The real importance of this is that the nonspecific binding is likely to be different for different coupled allergen preparations. Patient samples with highly elevated total IgE levels can exacerbate this problem. Because of this, some assays have adapted a conservative global cutoff of approximately 50 to 100 SDs above the mean of negative samples.<sup>18</sup> This may risk reporting an increased number of false-negative results but was done because very low levels of s-IgE are not believed to have a large clinical consequence.<sup>42</sup> A number of assay formats have chosen to use a low cutoff that increases the likelihood of reporting increased numbers of false-positive results.<sup>15,16</sup> Because most data comparing the different s-IgE assays have been analyzed in a dichotomous fashion (yes/no), considerations of cutoff selection, although likely to be trivial in a clinical setting, have produced the impression that highly significant analytical and clinical differences exist among the different test formats for different allergens. These statements gain more significance when test performances have been compared with other standards (eg, skin testing) whose false-positive and false-negative rates have been assumed and not scientifically established as discussed herein.<sup>43</sup>

## CLINICAL STUDIES

Clinical and analytical studies have differed widely in their conclusions as to the performance of tests for s-IgE. In

analyzing a number of these studies, it becomes clear that their conclusions depend on the testing method used, the allergen(s) studied, patient selection, and, most importantly, the standards used for comparison. For example, when s-IgE was measured to purified codfish allergen by the Phadebas RAST, the test results identified all the clinically positive and negative patients correctly (100% sensitive and specific).<sup>44</sup> However, performance of the Phadebas RAST and other test formats were shown to be less accurate with a number of other allergens, particularly when judged in comparison to the skin test.<sup>45</sup> Early in Europe, a concerted effort was made to make tests, such as the skin test, bronchial provocation, and s-IgE measurements, agree.<sup>26</sup> This was accomplished by adjusting the s-IgE assay's cutoff and skin test allergen extract strengths accordingly and is one explanation of why European studies have generally demonstrated better agreement among these different diagnostic modalities than those performed in the United States. However, most studies have demonstrated respectable diagnostic performance of s-IgE testing, but this has been better for some allergens and test formats than others.<sup>23–29</sup> More recent studies have demonstrated sensitivity, specificity, and predictive values greater than 90% for certain test systems documented with several thousand patients.<sup>37</sup>

To understand the nuances and interpretation of the clinical studies, it may be instructive to consider some fundamentals of how these studies are performed. Clinical sensitivity and specificity are determined by comparing an assay's results to a clinical standard. A large problem in allergy exists here because no well-studied clinical standard has actually been established.<sup>22,43,46</sup> In the past and present, numerous studies have used the clinical history evaluation as a standard with or without other tests, such as the skin test. The possibility that this process has been misleading has recently come to light. This is because the history is mostly a subjective judgment and as such susceptible to a number of heuristic errors. These errors depend on which allergen is under consideration and often consist of a bias toward false-positive diagnoses.<sup>43</sup> Thus, when a particular test agrees well with the history, the possibility is considerable that it also contains a false-positive component. This realization suggests that a great deal of the published literature in this field is not necessarily accurate in examining the clinical sensitivity and specificity of these tests. In addition, since these conclusions have resulted in the strong perception that the skin test is more sensitive than well-performing s-IgE tests, this conclusion should also be considered as mostly uncertain for similar reasons.

## PRESENT

Today, only a handful of the once commercially developed assays still exist. Unfortunately, a few of these still do not compare well to an analytical ideal standard.<sup>30</sup> Allergists should be aware of this in both studies and clinical practice. It is comforting that most of today's laboratories and manufacturers are governed by vigorous rules and regulations

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directing how these tests are manufactured and performed, including quality assurance measures, licensing, and proficiency testing. These measures consist of adherence to demanding requirements of the Clinical Laboratory Improvement Act of 1988 (CLIA 88) and approval requirements by the Food and Drug Administration (FDA). Unfortunately, laboratories that produce their own reagents and procedures are not covered by FDA licensing but are required to adhere to CLIA 88 principles and inspections. In addition, FDA licensing is not a perfect process, since performance requirements are often based on previously licensed tests (predicate devices). They also depend on clinical studies that are less than perfect for the reasons outlined herein. Thus, the quality of s-IgE tests is largely under the purveyance of the manufacturers. There are impressive guidelines published in a consensus document of the National Clinical Chemistry Laboratory Standards that outline a number of methods for manufacturers and users alike to ensure standardization and quality in production and use of s-IgE tests.<sup>40</sup> This document also sets suggested limits of variation (15% coefficient of variation) and describes methods to determine quantitative parameters. In addition, most laboratories that perform s-IgE tests participate in proficiency testing of blinded samples. Such tests reflect the interlaboratory precision of these tests.

Although many of these measures deal with laboratory and manufacturer reproducibility, they unfortunately do not necessarily ensure accuracy. The proficiency testing schemes come close to this but are limited in scope, participation of laboratories is not yet an absolute requirement, and results are based on consensus rather than an actual standard. At any rate, with the extent of regulation and economic pressures, most of the surviving s-IgE tests are considerably improved over what had existed before them.

## INTERPRETATION

Notwithstanding the confusion generated by some analytically inferior tests, comparisons to questionable standards, arbitrary cutoff determinations, and variable results for different allergens, there is little doubt that s-IgE testing is now on firm ground. Reasons for this include substantial improvements in some of the test methods and the very strong (but not perfect) association of s-IgE with allergic symptoms. For example, recent studies have confirmed the association of different levels of s-IgE with the degree of allergen exposure and the development of symptoms.<sup>47</sup> With respect to food allergies, quantitative s-IgE test results have been successfully expressed as the probability of a patient reacting to exposure.<sup>48–50</sup> Here, high-risk patients with high levels of s-IgE were shown to have a high probability of reactivity on exposure to those certain foods, whereas lower levels were associated with a lower probability. For different allergens, slightly different probabilities of reactivity have been associated with different levels of IgE antibody.<sup>51</sup> The reporting of s-IgE test results as probabilities or risk factors makes good sense, because it obviates the use of assay cutoffs and sup-

plies better information that can be integrated into the clinical picture. One problem with s-IgE tests that is often pointed out is the fact that individuals necessarily produce some s-IgE before expressing clinical symptoms.<sup>52</sup> As a result, the possibility exists that these individuals are sensitized but not necessarily clinically sensitive to the allergen(s) in question. Information on low levels of s-IgE may, however, be taken in a prognostic manner, indicating that continued exposure to these allergens may eventually lead to clinical reactivity.<sup>47</sup> Again, the clinical and exposure history of each patient must be taken into account for proper test result interpretation.

A possible confounder in the interpretation of s-IgE testing is that some allergens seem to be more potent or have different effects than others. Thus, multisensitized individuals would not be expected to react equally to the exposure to different allergens.<sup>52</sup>

By becoming aware of the quantitative level of a patient's s-IgE to different allergens, physicians can easily ascertain those allergens that are more likely to be causing symptoms. This type of information (allergic profiling) coupled with a clinical evaluation can be invaluable in defining major allergic problems.

Specific IgE testing has also been shown to have a predictive element. For example, sensitization to mite in early infancy has been demonstrated to account for a 3.4- to 19.7-fold risk for the development of asthma.<sup>53</sup> This is also related to the degree of exposure, and thus s-IgE testing early in life may lead to the instigation of avoidance measures that may reduce symptoms, the degree of sensitization, and the further development of symptoms.<sup>54–56</sup> As another example, the presence of s-IgE to egg at birth was shown to have a predictive value for the development of asthma of 95%.<sup>57</sup>

It is currently believed that s-IgE must be bridged by allergen to cause mediator release from inflammatory cells. In s-IgE assays the potential of bridging is not measured. Thus, it is possible that positive s-IgE assays may be detecting s-IgE that is nonfunctional. Again the value of detecting this type of s-IgE is likely to be prognostic, because these nonbridging IgEs can present allergens to the immune system, resulting in more s-IgEs directed toward different epitopes of the same allergen.<sup>58</sup> Presumably, when these are produced in sufficient amount and number, they will allow bridging with a better likelihood of initiating clinical symptoms on exposure.

There are still limitations in our knowledge of how to interpret s-IgE test results, since the clinical manifestations of allergic disease include a number of unknown variables. This is why it is paramount to interpret the results of s-IgE tests with full knowledge of exposure and the patient's clinical history. Allergists are best trained to establish this knowledge, but since many (particularly in the United States) have been reluctant to use these tests, this body of knowledge has been slow to develop. The fact that well-characterized, accurate, reproducible, and quantitative s-IgE tests are available

today for most allergens should certainly help to refine their use and application. In addition, the fact that specificity can be directly demonstrated for s-IgE tests certainly provides a distinct advantage over tests where this cannot be easily done (ie, skin test).

## CONCLUSION

The evolution of immunoassays for s-IgE has not been without controversy, some fair and some not so fair. Although s-IgE tests have contributed greatly to our understanding of allergic disease and the allergens involved, their acceptance has required resolution of a number of problems. These problems include a better understanding of the immunochemistry involved, a better knowledge of allergens, a better understanding of how to interpret test results, and the removal of some political and economic barriers.

Today, as the incidence of allergies seems to be increasing for largely unexplained reasons, it is clear that good objective tests are needed more than ever. With more than \$8 billion spent per year for care of allergic problems in the United States alone, it is apparent that good, cost-effective tools are necessary to ensure correct diagnostic information.<sup>59-62</sup> As physicians turn increasingly to evidence-based medicine, it is clear that well-performing s-IgE tests and their progeny offer the best chance for accuracy and objectivity in clarifying diagnoses and a number of distinct advantages that come with quantitative results.<sup>63</sup> Such tests also can be used to study and improve the efficacy of other diagnostic tests, pharmaceuticals, and treatment modalities so that these can be applied more effectively. As allergists and other physicians encounter patients with allergic-type symptoms, the accuracy and reproducibility of the s-IgE testing now available should continue to prove to be a valuable asset for our understanding and management of patients with allergic disease.

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Because of space limitations, all relevant studies in this field could not be cited. I apologize for any omissions. Comments regarding this article should be addressed to people with names such as Talmadge, Farr, Claman, DeWitt, Selner, Nelson, Sullivan, and Norman, whose addresses can be found in the list of great mentors.

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### **Self-Assessment Exam Questions**

1–5, Williams PB. 2003;91:518–524.

### **CME Test Questions**

1. The clinical sensitivity of the skin prick test compared with well-performing specific IgE (s-IgE) tests to identify patients with clinical disease is:
  - a. greater than that of s-IgE tests
  - b. less than that of s-IgE tests
  - c. dependent on the patients studied
  - d. dependent on the allergen selected
  - e. not scientifically established
2. Laboratories performing s-IgE testing to validate and document their performance are:
  - a. required to perform periodic proficiency testing
  - b. required to use Food and Drug Administration licensed tests
  - c. required to adhere to Clinical Laboratory Improvement Act of 1988 regulations
  - d. required to adhere to National Clinical Chemistry Laboratory Standards established criteria
  - e. all of the above
3. Conclusions for clinical studies on s-IgE testing depend on:
  - a. the s-IgE testing method used
  - b. which allergens are under consideration
  - c. which patients are selected for study
  - d. which standards are used for comparison
  - e. all the above
4. Specific IgE tests are available that are:
  - a. reproducible
  - b. accurate
  - c. quantitative
  - d. specific
  - e. all of the above
5. Information gained from s-IgE testing can be used for the following except to:
  - a. tell you if the patient is specifically sensitized to an allergen preparation
  - b. tell you how sensitive the patient is likely to be to a particular allergen
  - c. be used as a prognostic test giving information regarding evolving allergic disease
  - d. give information on treatment efficacy
  - e. tell you what symptoms the patient is likely to have on exposure

**Answers found on page 562.**

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