Allergen-specific IgE serologic assays define sensitization, not disease

(JANUARY 2016)

TO THE EDITOR: I read with great interest the commentary by Lau and Naugler[1] regarding how much allergen-specific immunoglobulin E (IgE) testing is too much. The authors made a number of important conclusions that directly contradict the international consensus statement on IgE antibody test performance published by the Clinical Laboratory Standards Institute (CLSI) in 2009 (2nd edition)[2] and updated in 2016 (3rd edition) in the I/LA-20 guidance document.[3]

The most important conclusion of the CLSI I/LA-20 panel was to reaffirm the golden rule of diagnostic allergy testing, which states that allergen-specific IgE antibody detected by either skin testing or serology methods is simply a marker for sensitization and thus only one of many risk factors for allergic disease. IgE positivity is not synonymous with the presence of allergic disease without a positive clinical history.[4] Clinicians, since the time that IgE was discovered as the reagin in 1967, have tried to use the presence of IgE antibody as detected either by skin testing or serology as the definitive indicator of allergic disease. This is simply inappropriate. Both skin testing and serology are diagnostic tests that indicate sensitization (the presence of IgE antibody) and not disease. The clinician using a positive clinical history of allergic symptoms, objectively collected, must make the link between sensitization (IgE antibody positivity) and allergic disease.

Lau and Naugler make this same mistake and conclude from their **Figure 1** data that "serum antigen-specific IgE testing is not a reliable diagnostic tool." They use the Wians criterion[5] of the summed diagnostic sensitivity and specificity of 170 to indicate if a test is clinically useful. They determined the sums of the diagnostic sensitivity and specificity for 89 allergen specificities, most of which they report as below 170. Among the specificities they cover are select aeroallergens, food allergens, venoms, and drugs. Importantly, they use a positive threshold of 0.35 kU/L for only some of their specificities, and they consider a sum of the diagnostic sensitivity and specificity equal to or greater than 170 as clinically relevant.

While Wians' analysis may have been appropriate for laboratory tests like glucose and even prostate-specific antigen that associate closely with defining a disease state, this criterion is inappropriate for IgE antibody tests that do not directly identify allergic disease. There is peer-reviewed literature on nonreactors based on their clinical history with a validated positive IgE skin test, IgE antibody serology, or food challenge tests.[6,7] Thus, the data in their **Figure 1** have no value in defining the performance of IgE antibody tests of sensitization.

Moreover, their report is vague on the actual IgE antibody assay method that was used. This information is important because we know that different IgE assay methods measure different populations of IgE antibody.[2,3] Also, the report does not define whether the participants who provided sera for testing actually had physician-defined allergic disease based on an objective clinical history.

The act of determining optimal cutoff values to maximize the "diagnostic" sensitivity and specificity is appropriate for many laboratory tests, but for allergen-specific IgE antibody analyses, it should be considered inappropriate. These are tests of sensitization, not disease. The IgE antibody result should be reported down to the regulatory-cleared and manufacturer-defined analytical sensitivity, which for the principal IgE antibody autoanalyzers used worldwide is 0.1 kU/L.[8] These concerns essentially invalidate the conclusions of their report. Unfortunately, they leave the reader with misleading negative impressions about the utility of IgE antibody analyses that are extensively validated methods.

Finally, contrary to the assertions of the authors, current commentaries on the topic of relative diagnostic performance of skin testing and autoanalyzer-based IgE serology tests support the conclusion that, especially for aeroallergens, both the in vivo skin test and the current autoanalyzer-based in vitro

serology tests provide overlapping, indistinguishable, and thus comparable diagnostic sensitivity and specificity results.[9,10] Unfortunately, the authors refer to the 2008 Bernstein practice parameter that is out of date in relation to autoanalyzer technology, which has advanced by 2016.

Thus, contrary to the assertions of Lau and Naugler, IgE antibody serology has a clear, well-defined, and positive role in defining sensitization as a key part of the diagnostic workup of a patient who is suspected of having allergic disease. As with any laboratory test, IgE antibody measurements need to be judiciously ordered and used by the clinician only when there is a strong pretest likelihood, based on the patient's clinical history, of allergic disease.

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doi:10.3949/ccjm.83c.05001

IN REPLY: We thank Dr. Hamilton for his interest in our article and for providing more recent literature than was available at the time we submitted our manuscript.

There are multiple points of view toward allergy testing. But the bottom line, as emphasized by Dr. Hamilton and in our article, is that serum IgE testing should not be used as the sole diagnostic tool because it is an indicator of sensitization, not disease, and that clinical history should always be used in conjunction to ensure proper diagnosis.

It is our experience that some clinicians indiscriminately order large panels of serum IgE tests. As Dr. Hamilton indicates, patients can have positive serum IgE results but not display allergy symptoms, which can lead to unnecessary food avoidance. In addition, false-negative results from injudiciously ordered tests (ie, not based on pretest probability) can lead to missed diagnoses. All of these points should be kept in mind in delivering good clinical care, and as such, Choosing Wisely has highlighted the importance of using this test appropriately.

In response to the origin of the sensitivities and specificities used to calculate the sum, the values were curated from available literature and thus limited the number of allergens that could be profiled. A cutoff of 0.35 kU/L was used because this was the cutoff used by the references.

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doi:10.3949/ccjm.83c.05002