

Letter to the Editor

Clinical laboratories worldwide need to report IgE antibody results on clinical specimens as analytical results and not use differential positive thresholds

To the Editor:

I have followed with great interest the discussion between Scala and Sopo¹ and Tripodi et al² related to the appropriate threshold that should be used in reports of serologic testing to define a positive allergen-specific IgE antibody level. Should it be 0.7, 0.35, or 0.1 kU_A/L? The use of a variable positive threshold for research studies³ in which receiver operator characteristics curves are used is understandable. However, when IgE antibody results are reported on clinical serum specimens for use in the diagnostic workup of a patient, the same defined negative/positive cutoff should be used by all clinical immunology laboratories worldwide when using a particular assay method. This approach would treat the IgE antibody measurement as an analytical measurement that it is instead of suggesting that it inherently has value in defining the presence of allergic disease.

This issue has become a problem for clinicians practicing in the United States. It has recently been noted that 47.6% of approximately 300 participants (among them federally licensed clinical laboratories) in a widely subscribed external proficiency survey⁴ report allergen-specific IgE results only down to a historical cutoff of 0.35 kU_A/L. Thus, for some laboratories, IgE antibody level of less than 0.35 kU_A/L is reported as an undetectable result. In contrast, 34.1% of the participants currently report IgE antibody results down to the US Food and Drug Administration–cleared analytical sensitivity of 0.1 kU_A/L. This makes IgE antibody levels of less than 0.1 kU_A/L undetectable for these laboratories. The remaining approximately 18% of the participants in the survey report that they use different positive/negative cutoff levels. One confounding variable in the use of these data is that they were generated using responses from laboratories using a number of different US Food and Drug Administration–cleared IgE antibody singleplex IgE antibody assays. Interestingly, 10% of the participants in the survey indicated that they could actually report a “positive predictive value” or the level of IgE antibody above which they considered allergic disease was likely. The concerns raised by Scala and Sopo,¹ addressed by Tripodi et al,² and discussed in the US data set⁴ are troubling because they emphasize the continued widespread use of differential reporting schemes for allergen-specific IgE antibody. Clinical laboratory directors who perform diagnostic allergy testing, particularly in the United States, do not appear to understand the limitations of the allergen-specific IgE result that must be viewed within the context of patient’s history to be of any clinical value. Allergen-specific IgE antibody whether measured in the blood by serologic assays or in the skin by puncture or intradermal skin test techniques is simply an indicator of sensitization (IgE antibody positivity) to a particular allergen specificity.⁵ It does not by itself define allergic disease, no matter how many “predictive” probability of disease versus IgE antibody concentration plots are reported by investigators for different allergen specificities. IgE antibody positivity is simply one of many risk factors that need to be factored into the decision process by the practicing clinician when they combine diagnostic test results with their patient’s history and physical examination data. Historically, 0.35 kU_A/L was

the reported IgE antibody threshold (medical decision point) that was used to identify individuals with “clinically evident allergic disease.” In recent years, a lower limit of quantitation for clinically used autoanalyzer-based IgE assays, which has been blessed by regulatory agencies, has been assigned as 0.1 kU_A/L. This has resulted in IgE antibody levels that are reported between 0.1 and 0.35 kU_A/L, which will not always correlate with clinically evident allergic disease. To illustrate the value of IgE antibodies in this range, Linden et al⁶ showed using Youden plots that optimal performance (diagnostic sensitivity and specificity) of cat and dog specific IgE antibody levels was achieved in their study at 0.12 and 0.2 kU_A/L, respectively, with a widely used singleplex assay. However, in general, IgE antibody levels between 0.1 and 0.35 kU_A/L must be cautiously interpreted by the clinician within the context of clinical symptoms because their clinical significance remains unknown. A recommendation to clinical laboratories by a 2015 consensus guidance document on this issue⁵ is that all clinical laboratories report their IgE antibody results as analytical measurements down to the regulatory accepted *lower limit of quantitation* of the assay (also known as the assay’s “analytical sensitivity”). For the United States, this is 0.1 kU_A/L for the 3 principal singleplex autoanalyzers. Then, the clinician may incorporate the IgE antibody results with environmental exposure, patient history, physical examination, and other relevant data to derive a likelihood of allergic disease. Clinical laboratories need to provide analytical measurements of IgE antibody that are as close to “truth” as technically achievable by their assay system and then let the clinician judge the measurement’s utility in making the diagnosis. This is the recommended approach rather than each laboratory *a priori* deciding in a different way for the clinician on what the laboratory considers a “clinically relevant” positive threshold on the basis of limited and often subjectively collected data. Changes to this differential use of lower limits of quantitation will occur only when the requesting physician who orders IgE antibody analyses during a diagnostic workup of their patients requires that their clinical laboratory report uniform analytical sensitivity sanctioned by the manufacturer and regulators. As part of global harmonization of analytical methods, use of a uniform lower limit of quantitation is especially important for physicians who receive reports generated by different laboratories across the globe that use the same IgE antibody assay system. One goal of the International Standards Organization/Clinical Laboratory Standards Institute consensus guidance documents is the worldwide use of harmonized IgE antibody assay working ranges and limits of quantitation so that a report generated anywhere in the world will provide the same analytical data for interpretation by the clinician.

Robert G. Hamilton, PhD, DABMLI

From the Division of Allergy and Clinical Immunology, Departments of Medicine and Pathology, Johns Hopkins University School of Medicine, Baltimore, Md. E-mail: rhamilt2@jhmi.edu.

Disclosure of potential conflict of interest: The author declares that he has no relevant conflicts of interest.

REFERENCES

1. Scala G, Sopo SM. When are serum specific IgE levels positive? *J Allergy Clin Immunol* 2015;135:291-2.
2. Tripodi S, Caffarelli C, Stringari G, Dondi A, Asero R, Matricardi PM. Reply: To PMID 24794684. *J Allergy Clin Immunol* 2015;135:292-3.

3. Stringari G, Tripodi S, Caffarelli C, Dondi A, Asero R, Di Rienzo Businco A, et al. The effect of component resolved diagnosis on specific immunotherapy prescription in children with hay fever. *J Allergy Clin Immunol* 2014;134:75-81.
4. Diagnostic Immunology Resource Committee. SE-B 2014 Diagnostic Allergy Survey Participant Summary. Northfield, Ill: College of American Pathologists; 2014.
5. Hamilton RG, Matsson P, Hovanec-Burns DL, VanCleve M, Chan S, Kober A, et al. Analytical performance characteristics. In: Quality assurance and clinical utility of immunological assays for human IgE antibodies of defined allergen specificities (CLSI-Guidance Document ILA20-A3). Wayne, Pa: Clinical Laboratory Standards Institute; 2015.
6. Linden CC, Misiak RT, Wegienka G, Havstad S, Ownby DR, Johnson CC, et al. Analysis of allergen specific IgE cut points to cat and dog in the Childhood Allergy Study. *Ann Allergy Asthma Immunol* 2011;106:153-8.

<http://dx.doi.org/10.1016/j.jaci.2015.03.002>