

Reprinted Courtesy of CAP Today,
a newsmagazine published by the
College of American Pathologists
All rights reserved
www.cap.org



(A)topic of concern: omitting specific IgE tests

Published: March 2007, Feature Story

By Anne Ford

Call it the no-brainer of the week: If a patient comes to her primary care physician and reports frequent urination, extreme thirst, and a family history of diabetes, what is the appropriate clinical response?

"I would never say to the patient, 'You might have it [diabetes]. Take this medicine, see me in a month, and I'll see how you're doing,'" said Leonard Fromer, MD, an allergist and family physician from Santa Monica, Calif.

"It's pretty clear that for most of the atopic disease presentations, we're doing a lot of, 'Try this and see if it works,' rather than using specific IgE testing to 'make an informed, evidence-based decision.'"

But that's more or less what many clinicians do when diagnosing patients with allergies, he asserts. "It's pretty clear that for most of the atopic disease presentations, we're doing a lot of, 'Try this and see if it works,'" rather than using specific IgE testing to "make an informed, evidence-based decision," Dr. Fromer said.

In "Advances in IVD Allergy Testing"—a recent audioconference offered by the American Association for Clinical Chemistry—Dr. Fromer and P. Brock Williams, PhD, clinical research professor, allergy and clinical immunology, at the University of Missouri, Kansas City, discussed the importance of specific IgE measurement and its potential to enhance patient care.

"Despite the fact that medically significant allergies are becoming more widespread," Dr. Williams said, "most cases are still diagnosed simply on the basis of medical history, perhaps medication challenges, clinical symptoms, and skin testing or food challenges." The complexity of allergy as a disease, he pointed out, makes this approach less than ideal: "The symptoms are quite common and have a number of other different causes that are not mutually exclusive. There are primary and secondary inflammatory effects and...temporal relationships with exposure, but sometimes these temporal relationships aren't completely clear."

In addition, most allergy patients are sensitive to more than one allergen, and untreated allergic symptoms can result in serious, even fatal complications such as anaphylaxis. Add to that an estimated \$17 billion in annual allergy-related health care costs, and the value of objective specific IgE testing becomes even more apparent.

Those costs stem in part from what Dr. Fromer calls "the allergy march," that is, the symptom progression of many atopic patients. They often begin life as infants with eczema,

then turn into toddlers with food allergies, older children with recurrent ear infections, preteenagers with rhinosinusitis, and ultimately, adolescents and adults with asthma. That progression, Dr. Fromer says, "is played out against the exposure to triggers, which very much determines the consequences in terms of clinical signs and symptoms. If we know what the triggers are...[and] teach the patients to get below their symptom threshold for those triggers, we can greatly modify the expression of that gene in these patients."

He points out, too, that there are 21 million asthmatics in the United States and that asthma is overwhelmingly an allergic disease. "The NIH asthma guidelines...speak towards this and speak towards using testing, either in vitro serum IgE or on the skin, to identify persistent asthmatics and their triggers."

So why are some clinicians slow to recognize the value of specific IgE testing? As Dr. Fromer acknowledged, "A lot of them say, 'Why do we need to test a patient if they walk in and say they absolutely positively know it's ragweed, or they know it's cats, or they know it's dust?' Well, the answer is, even though they may be right about that trigger, that's not the complete story." For example, patients who can tell they're sensitive to ragweed may be unaware that they're sensitive to several other allergens as well, which don't produce symptoms until they're exacerbated by the presence of ragweed.

'Why do we need to test a patient if they walk in and say they absolutely positively know it's ragweed, or they know it's cats, or they know it's dust?' Well, the answer is, even though they may be right about that trigger, that's not the complete story."

Furthermore, the likelihood of a patient obtaining a prescription for allergy medication is often driven to an inappropriate degree by the preference of that patient, Dr. Fromer said.

"... A 2004 study... found that 65 percent of patients who requested allergy medication from their physicians and had been placed on a nonsedating antihistamine were on the wrong medication. They were not atopic and had other etiologies for their allergy-like symptoms."

Direct-to-consumer advertising, the prevalence of medical information on the Internet, and the current allergy epidemic have produced patients who are "convinced they have allergies if they have symptoms from the neck up, and they want medication." He cited a 2004 study that found that 65 percent of patients who requested allergy medication from their physicians and had been placed on a nonsedating antihistamine were on the wrong medication. They were not atopic and had other etiologies for their allergy-like symptoms (Szeinbach SL, et al. *J Manag Care Pharm.* 2004; 10(3): 234-238).

Clinicians making an allergy diagnosis over-rely, too, on patient history, Dr. Williams said. He used decision theory to explain why patient history should not be considered the gold standard for diagnosis. First, simply because patients have gone to an allergist, the unconscious assumption is that they must therefore have allergies, when that may not be the case. Second, "a lot of times someone will anchor to one particular item in the history and then not pay attention to anything else," he said. In addition, the so-called availability error means that physicians sometimes make the mistake of thinking that, for example, if Patient A is allergic to pollen, Patient B resembles Patient A, and the pollen count is high, Patient B must be allergic to pollen. Finally, fear of missing something in a patient's history makes some physicians more likely to overpredict the number of allergens to which the patient is sensitive.

In a 2003 study, Dr. Williams and his coauthors compared patient history with concordant skin tests and specific IgE measurements to seven common allergens (*Ann Allergy Asthma Immunol* 2003; 91: 26– 33). They found that history and physical examination alone rarely exceeded 50 percent accuracy. “That’s essentially flipping a coin,” Dr. Williams pointed out.

“History and physical examination alone rarely exceeded 50 percent accuracy.”

But what about other methods? Allergen provocation testing is somewhat cumbersome and not particularly accurate, Dr. Williams said. Medication trials overlook the fact that many medications are nonspecific, have side effects, or are not particularly effective. “There have been studies on Claritin that showed that it’s only three percent over placebo,” he pointed out, “and so a medication trial is obviously not going to give you a good answer on that.” And as for prick and other dermal tests, “they essentially are not standardized, the extracts

“Specific IgE tests stand out as ‘the only tests in this group that are actually objective.’”

are not defined, the methods differ, even the devices differ in different offices. There are interpretive problems, and we really don’t know what the rate of false positivity or false negativity or the sensitivity or the specificity of the skin tests actually are.” Against this dismal backdrop, specific IgE tests stand out as “the only tests in this group that are actually objective.”

Dr. Williams summarized the history of IgE testing: “From ‘74 to ‘92, we saw quite a few different varieties of tests for IgE on the commercial market. And these all involved a lot of differences. These differences included different sources of allergens, the allergen extracts, there were different coupling chemistries introduced, different solid phases. The detection using enzymes as opposed to radioisotopes was introduced, along with monoclonal or mixtures of monoclonal antibodies to improve the specificity of the test. And all these tests worked, but not to the same extent. Unfortunately, all these tests were referred to as RAST [radioallergosorbant] tests...which is very unfortunate, because it doesn’t distinguish between tests that perform well and not so well,” he said.

The most gratifying part of current IgE efforts, he added, “is that where the real progress is being made, we are now generating risk ratios and probability curves that are related to the specific IgE a patient has in their serum.”

In 2001, Dr. Williams and three coauthors conducted a study of three specific IgE testing methods (*Ann Allergy Asthma Immunol* 2001; 86: 373–381). “We had an n of 12,708 results, which we analyzed for precision, accuracy, and quantitative ability for each allergen in the study,” Dr. Williams said. The authors discovered that the three methods varied widely in their precision, which they measured by the percent CV of triplicates of the positive responses: “For some allergens the precision was not that bad, and some it was quite bad.” Why is this important? “Well, we’ve now come to understand that the level of specific IgE in the serum is certainly related to the probability of an individual having symptoms when they’re exposed to that particular allergen,” he said. “If you have a CV of around 25 percent, then that essentially covers a very large part of this curve and makes it very difficult to use this relationship.”

A year before, Dr. Williams and three coauthors had published a study on the accuracy and quantitative ability of three IgE methods via dilutional analysis (*J Allergy Clin Immunol* 2000; 105: 1221–1230). Quantitation is important, Dr. Williams said, “because we can now relate the amount of IgE antibody people are producing to the probability that they’re

having symptoms." In this regard, the questions to ask are: Are dilutions of samples parallel to the calibrator? Does this occur over the stated range? If so, is this true for all allergens? What is the standard used for comparison? Can an imprecise assay be quantitative?

The study authors discovered that on a dichotomous basis, the methods agreed fairly well. "However, if we look at a logarithmic Bland-Altman plot, which is essentially taking one [method] as a standard and comparing the other two results across the assay range, we can show...that the results are not similar at all," Dr. Williams said. "We don't know which one is right from this analysis, but we can certainly say that for any of these assays, the results do not correlate very well with the other assays." Conclusion: Results from the different assays cannot be used interchangeably, and studies on clinical interpretations must be performed for each method alone.

To determine which assay produced the best results, the study authors used chimeric antibodies, that is, humanized mouse monoclonal antibodies with the human IgE constant portion of IgE and specificity for the major allergens of mite and birch. "We found that one assay essentially correlated very well with the standard," Dr. Williams said. "But we found one assay essentially did not report very much specific E for any of these dilutions, whereas one assay way overestimated the amount of IgE in these samples."

"I might point out," he added, "that if you took any of these curves by themselves, they look fairly linear. So people can publish curves that look like they are linear and giving good quantitative results, but until they compare it to a standard such as a chimeric antibody, they don't know if that linear curve is actually accurate or not. I would caution people to read the literature carefully and consider the source. We've seen clear-cut examples of selective use of data, improper use of statistics, publications in low-impact journals, which are generally not reviewed as vigorously as high-impact journals, leading to some rather questionable studies and the clear-cut fact that these are essentially marketing studies."

Finally, Dr. Williams advised participants to watch later this year for the updated version of a consensus document from the Clinical and Laboratory Standards Institute that delineates some of the characteristics of the specific IgE tests and the kind of proficiencies they should

"The scoring of the specific IgE is either quantitative or semiquantitative, whereas the skin test is really very subjectively graded from a one plus to a four plus.

meet. "There's nothing like this for skin testing," he pointed out. "The scoring of the specific IgE is either quantitative or semiquantitative, whereas the skin test is really very subjectively graded from a one plus to a four plus. It's really nice that with the specific IgE test you can actually show that you're measuring what you think you're measuring, so we can show specificity and we can show analytical sensitivity in how sensitive these assays are, with statistics, and neither of these are known for skin testing."

Dr. Fromer, meanwhile, ended by emphasizing how specific IgE testing can contribute to a new health care paradigm of evidence-based treatment. Too often we immediately "throw medicine at people," he says. In the case of allergies, that often means neglecting to use specific IgE testing to help allergy patients determine their triggers so they can, if possible, minimize their exposure to them. "We go right past available objective testing, in this case right past IgE, right past lifestyle change," he says. "It makes no sense. We have to get away from that. We have to use the tools we have—that is, IgE—to get evidence, to do better for the patients."