

Reflections on current food allergy controversies: Specific IgE test application, patch testing, eosinophilic esophagitis, and probiotics

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ABSTRACT

This presentation addresses four selected issues that are current controversies in the area of food allergy. First, the diagnostic proficiency of specific IgE (sIgE) measurement. sIgE testing has been a useful screening test; the higher the level, the more likely to be clinically relevant. However, published predictive values varied from one study to another. Levels derived from data on certain groups of patients reflect probabilities that can not be applied with certainty to individual patients. Several factors need to be considered in interpreting the value of sIgE in any particular patient. Definitive decisions require well-designed challenge testing. Second, a few studies suggested the usefulness of including patch testing in food allergy evaluation. It may reveal positive results that may or may not be clinically relevant. At present, its use is not generally accepted because of inconsistency in the reported findings and the lack of standardization of test materials and interpretation. It may possibly have a role in evaluating eosinophilic esophagitis (EE) more than in atopic dermatitis. Third, EE does not seem to be a new disease or is causing a miniepidemic. Its increasing diagnosis is probably because of a greater awareness and better biopsy assessment. Fourth, the usefulness of probiotics on allergy prevention or treatment has been reported by some studies but not by others. Appropriately designed studies are needed to identify the efficacious type(s) of probiotics, effective doses, method of administration, optimal time to begin, and duration of therapy.

(Allergy Asthma Proc 29:447–452, 2008; doi: 10.2500/aap.2008.29.3150)

Key words: Atopic dermatitis, eosinophilic esophagitis, food allergy diagnosis, food allergy prevention, food allergy treatment, IgE antibodies, *in vitro* allergy testing, patch testing, probiotics

Controversy in science is a healthy phenomenon through which sound conclusions can be reached. Out of several controversial issues in the area of food allergy, I elected to address four that I think are currently relevant to clinical practice: specific IgE (sIgE) antibody testing, the usefulness of food patch testing, the emerging eosinophilic gastrointestinal disorders, and the use of probiotics. Published data on each of these issues will be summarized in a balanced way in an attempt to answer the following specific questions:

1. Can food sIgE testing obviate the need for challenge testing?
2. Should patch testing be included in food allergy evaluation?

3. Is eosinophilic esophagitis (EE) a new disease, and is it caused by food allergy?
4. Is there a place for probiotics in allergy practice?

CAN FOOD sIgE TESTING OBVIATE THE NEED FOR CHALLENGE TESTING?

Using retrospective data, Sampson and HO in 1997 published sIgE levels measured by the ImmunoCAP system (Pharmacia Diagnostics, currently Phadia AB, Uppsala, Sweden) that may be predictive of common food allergies based on double-blind challenge testing or convincing medical histories.¹ All subjects were children (aged 0.6–18 years) with atopic dermatitis (AD). They noted that the 90 and 95% predictive sIgE levels varied widely among the six common foods tested. The 95% positive predictive level was 6 kU/L for egg, 15 kU/L for peanut, 20 kU/L for fish, and 32 kU/L for milk allergy, but was poor for soy and wheat. Later, those levels were applied by the same authors on a group of children (ages 0.4–14.3 years) with AD in 61% and asthma in about one-half and were found to be of high positive predictability.² However, a close look at the second study data by itself showed predictive levels that are different from the first study, except for fish, and varied widely among the foods tested. In neither study was the total IgE level nor the reaction's severity accounted for in the data analysis.

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Presented in part at the combined meeting of the Southwest Allergy Forum, Texas Society of Allergy, Asthma and Immunology, and Eastern Allergy Conference, Puerto Vallarta, Mexico, January 16–19, 2008

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Table 1 Factors to be considered in interpretation of food-specific IgE level

Total IgE level
Patient's age
Type of allergy manifestation
Severity of allergy manifestation
Food allergen
Degree of exposure to the food being tested
Duration of avoidance of that food
Proficiency characteristics of the assay

Different findings were reported by others³⁻⁵ and may be due to several differences between the studied patients groups. For example, several studies reported that the sIgE level at 95% positive predicted value in infants are much lower than in older subjects.^{3,4,6}

According to a large study on peanut and tree nut allergy,⁴ the CAP-IgE test result was "falsely negative" in 22% of allergic patients and was "falsely positive" in 40% of nonallergic subjects. Only 30% of patients with the most severe reactions had an sIgE level of ≥ 15 kU/L. In at least three studies on subjects suspected of having food allergy,^{5,7,8} sIgE levels in allergic subjects (positive challenge test) showed a remarkable overlap with those in subjects who had a negative challenge. In a follow-up study⁹ on food-allergic children <4 years, when sIgE level decreased within 1 year to even 10% of the initial level, 22% were still intolerant to egg and 34% were still intolerant to milk.

The foregoing findings indicate that sIgE level has suboptimal predictive values. This should not be surprising because the test identifies circulating IgE antibodies that may not quantitatively correlate well with the sIgE antibody bound at the target tissue. In clinical practice where decisions are made on individual patients, the application of probabilities would be associated with errors that can have substantial consequences. Certainty would require well-designed food challenge testing.¹⁰ Like skin testing, sIgE measurement remains a useful screening test but its level should be interpreted according to several coexisting factors (Table 1). It is worth noting also that sIgE levels measured by different assays are not comparable.¹¹

SHOULD PATCH TESTING BE INCLUDED IN FOOD ALLERGY EVALUATION?

Allergy patch testing (APT) has been traditionally used to identify allergens that cause reactions through T-cell-mediated hypersensitivity (type IV). The typical example is allergic contact dermatitis, which is mostly evaluated by dermatologists. A recent survey¹² showed that APT is infrequently used by allergists and that a majority desire to introduce the test to their practice. Such a recent trend might have been gener-

ated by an increasing interest in contact dermatitis evaluation and by the emerging literature on using APT in evaluating hypersensitivity reactions to foods, particularly in patients with AD where T cells play a significant role in the pathogenesis.

In 1996, Isolauri and Turjanmaa reported a comparison between skin-prick testing (SPT) and APT in children with AD and milk allergy.¹³ They noted that immediate reactions to challenge were associated with more positive SPT whereas delayed reactions were associated with more positive APT. Accordingly, perhaps a combined use of SPT and APT might enhance the identification of the offending food(s). In another study on children with various symptoms to milk allergy, the positive predictive value of APT was higher than that of SPT for both immediate (87% versus 73%) and late reactions (60% versus 22%).¹⁴ However, in another study on children with AD, the APT did not identify an offending food that was not identified by SPT.¹⁵

A few studies addressed the potential usefulness of food APT in patients with EE. In a series of 26 children with EE,¹⁶ positive tests were slightly more frequent by APT (21) than by SPT (19), and not necessarily to the same foods. APT was positive in 6 of 7 instances of negative SPT, and SPT was positive in 4 of 5 instances of negative APT. Similar findings were observed in a larger series.¹⁷ Therefore, using the combination of SPT and APT seems to be superior to either alone in identifying the offending foods in patients with EE. However, using both tests might identify more foods as positive, but may not be clinically relevant, because only 7% of food test results was positive by both SPT and APT. Furthermore, in addition to the lack of standardized food material for APT, the test has significant problems in its application and interpretation, particularly in patients with concomitant AD.¹⁸

IS EE A NEW ALLERGIC DISEASE AND IS IT CAUSED BY FOOD ALLERGY?

Eosinophilic gastrointestinal disorders are being increasingly recognized.¹⁹ The esophagus is the most common site, but the stomach, small intestine, and colon can be affected. The onset is primarily during childhood and progresses into adulthood with marked predominance in males. The clinical manifestations can be dysphagia, gastroesophageal reflux, vomiting, abdominal pain food impaction, or intestinal bleeding. Endoscopy may reveal esophageal rings, strictures, longitudinal furrows, and microabscesses or whitish plaques. Biopsy shows eosinophilic infiltrate in the mucosa, submucosa, and muscularis. The cutoff diagnostic level of mucosal intraepithelial eosinophils used by various authors as diagnostic varied from 15 cells/high power field (hpf) to 24 cells/hpf, at any hpf.^{17,20-22}

Is EE a New Disease?

Together with the increasing publications¹⁹ and presentations on EE during scientific meetings of allergy and gastroenterology societies, there has been a concern whether this is a new disease. Vanderheyden *et al.*²³ compared the findings in 150 esophagitis biopsy specimens obtained during May-June 2005 to the findings in 115 biopsy specimens obtained from different patients 15 years earlier. They found no difference between the two groups regarding the number of intraepithelial eosinophils; 7% in each group showed >20 eosinophils/hpf. The number of eosinophils/hpf in the biopsies ranged from 21 to 139 (mean, 56) biopsy specimens in 2005 and 26 to 156 (mean, 51) in biopsy specimens dated 15 years earlier. Therefore, it seems that EE is not a new disease and its recent increasing diagnosis is because of awareness, increased use of endoscopy, biopsy examination, and quantitation of the eosinophilic infiltrate. Probably, most EE cases in the past were misdiagnosed as gastroesophageal reflux disease.

Is EE Caused by Food Allergy?

The early age of onset of manifestations of EE and the very high incidence of atopy (~75%) strongly suggest an allergic etiology. Several studies showed that food hypersensitivity is involved and can be suspected by the medical history, sIgE measurement, skin-prick testing, or patch testing.

In 1995, Kelly *et al.*²⁴ reported the findings on 10 children (8 months to 12 years) with gastroesophageal reflux disease and EE who showed poor response to antireflux therapy, including fundoplication in 6. Within 2–6 weeks of feeding limited to an elemental formula, all 10 children showed remarkable improvement in symptoms and a decrease in esophageal mucosal eosinophils. Skin testing to foods and challenge were positive in nine children, most commonly to cow milk, soy, wheat, and peanuts. Elimination of the offending foods allowed discontinuation of the elemental formula and of the antireflux medications. Markowitz *et al.*²⁵ reported improvement in 49 of 51 children within 8 days on feeding limited to an elemental formula.

In 26 children with EE, Spergel *et al.*¹⁶ noted that 21 (81%) had dermatologic and/or respiratory allergies and positive skin test (prick or patch) to foods. Challenge was positive in 25 patients, most commonly to cow milk, eggs, wheat, soy, and beef. With 4–12 months of dietary elimination, 18 (69%) patients showed marked improvements in symptoms and a decrease in mucosal eosinophilic infiltrate. Similar findings were reported by several other studies.²⁶

In a retrospective analysis of data on 89 children with EE, Assa'ad *et al.*²¹ noticed that the age of onset of

symptoms ranged from 0.08 to 16 years, with a mean age of 3.4 years. There was sensitization to foods in 75% of cases, most commonly eggs, peanuts, soy, cow's milk, bananas, and mustard. Associated atopic diseases were asthma in 39%, rhinitis in 30%, eczema in 19%, and food-induced anaphylaxis in 9% of cases. Dietary elimination and swallowed aerosolized corticosteroid therapy resulted in resolution after an average of 11 months, but relapse occurred in 79%, indicating chronicity of the disease.

A few studies reported a high prevalence of aeroallergen sensitization in EE patients, particularly in older children and adults.^{21,27,28} The nature of this association has not been clarified because most EE patients have respiratory allergies that may be related to hypersensitivity to aeroallergens.

The foregoing data indicate that food allergy is a major factor in EE, although the offending food(s) may not be easily identified or dietary elimination alone may not bring total resolution. Preliminary data from a trial of humanized anti-IL-5 (mepolizumab) therapy in a small number of patients showed very promising results.²⁹

IS THERE A USE FOR PROBIOTICS IN ALLERGY PRACTICE?

Probiotics are components of the normal gut microbiota. They are live microbial food ingredients, the growth of which requires the availability of nonabsorbable, nondigestible carbohydrate food components referred to as prebiotics.³⁰ Probiotics are mostly nonpathogenic live bacteria that can survive the gastrointestinal environment and compete with pathogenic bacteria. Their beneficial effect to the host is through adherence to the intestinal mucosa and interaction with the gut-associated lymphoid tissue to stimulate immunity without inducing inflammation. Through cellular interaction and various cytokine production, probiotics influence Th0 cell development in favor of Th1 over Th2 pathway. Among many probiotic bacteria, *Lactobacillus* and *Bifidobacterium* species are the most common; the former resides primarily in the small intestine and the latter in the colon.

Information on the health benefits of probiotics has been gaining increasing interest among the public, health care providers, and the industry. In the field of allergy, studies on probiotics addressed their potential role in the areas of prevention and treatment.

Studies on Probiotics for Allergy Prevention

Kalliomaki *et al.*³¹ performed a study on 159 pregnant women with a history of atopy in the fetus' parents or siblings. At 2–4 weeks prenatally and for 6 months during lactation, mothers were given a placebo or *Lactobacillus* GG (10,000 CFU) daily. Nonbreastfed

infants were given the material directly. By 2 years of age, AD in the probiotic group was one-half as frequent as in the placebo group. The effect was independent of the method of administration, *i.e.*, through the breast milk or directly to the infant. A similar beneficial effect was reported by Rautava *et al.*³² who showed the presence of a higher concentration of the anti-inflammatory cytokine TGF- β in the breast milk of mothers who received *Lactobacillus*.

On the other hand, two recent studies did not support the aforementioned findings. In a study by Taylor *et al.*,³³ 218 newborns of atopic mothers were randomized to receive from birth until 6 months either a placebo or *Lactobacillus acidophilus* 3×10^9 daily. By 6 and 12 months of age, the AD incidence in the *Lactobacillus* group was similar to that in the placebo group. In fact, the probiotic group showed higher frequency of positive skin tests to common foods and aeroallergens than the placebo group. In another study,³⁴ expectant mothers of infants at high risk of atopy were given 2–4 weeks prenatally a mixture of four probiotics (two types of *Lactobacillus rhamnosus*, *Bifidobacterium*, and *Propionibacterium*). Their newborns were given a placebo or the probiotic mixture plus a prebiotic for 6 months. By 2 years of age, the two groups showed no significant difference in the cumulative incidence of any allergic disease or sensitization to common allergies. A study of three European birth cohorts showed no relationship between development of atopic eczema or food sensitization and the type of intestinal commensal bacteria.³⁵

Studies on Probiotics for Allergy Treatment

Majamaa and Isolauri³⁶ reported on a group of infants with AD and milk allergy who were fed an extensively hydrolyzed whey formula with or without *Lactobacillus GG*. After 1 month, the AD score markedly improved in the probiotic group (from 26 to 15) but not in the nonprobiotic group (from 21 to only 19). It also improved (from 26 to 11) in a third group of infants who were breastfed and whose mothers received *Lactobacillus GG* for 1 month. The infants who received the probiotic showed a reduction in fecal α -1-antitrypsin and tumor necrosis factor α , indicating alleviation of the intestinal mucosal inflammation. In a subsequent study by Isolauri *et al.*,³⁷ infants who developed AD while being exclusively breastfed were fed an extensively hydrolyzed whey formula with or without supplementation with *Lactobacillus GG* and *Bifidobacterium lactis Bb-12*. At 2 months, a significant improvement in the score of AD was noted in all nine infants who received probiotic supplementation, but in only four of nine infants who did not. A similar trend was noted by Rosenfeldt *et al.*³⁸ using a combination of *L. rhamnosus* and *Lactobacillus reuteri*. Another study³⁹ showed a

Table 2 Possible causes of the inconsistent findings published on the usefulness of probiotics in allergy prevention or treatment

Species and specific strain of probiotic
Dose used
The use of combination vs single type
Method of administration
The age at administration for prevention
The time after disease onset for treatment
Duration of administration
Coexistence of food allergy
Dietary elimination
Limiting feeding to a hypoallergenic formula

beneficial therapeutic effect of *Lactobacillus GG* but not by a mixture of *Bifidobacterium breve*, *Propionibacterium freudenreichii*, and *Propionibacterium IS*.

On the other hand, a study⁴⁰ on young infants with AD showed no advantage of adding *L. rhamnosus* or *Lactobacillus GG* to an extensively hydrolyzed whey formula. Neither was there a significant effect of probiotics on allergy markers (total and sIgE), inflammatory markers (peripheral eosinophilia, urinary eosinophil protein X, and fecal α -1 antitrypsin), or cytokine production by peripheral blood mononuclear cells. Another study showed no advantage of *Lactobacillus GG* over placebo in improving mild to moderate AD.⁴¹

In a group of children ≤ 10 years of age with AD, the daily intake of probiotic mixture of *L. rhamnosus* and *B. lactis* for 12 weeks did not differ from placebo in improving the score of AD.⁴² However, the improvement was significantly higher in the food-sensitized than in the non-food-sensitized patients, but the observed improvement was not sustained at 4 weeks after cessation of probiotics. In a recent study by Hol *et al.*,⁴³ young infants (1.4–6 months) with milk allergy were treated with extensively hydrolyzed formula supplemented with placebo or with *L. casei* plus *B. lactis*. Tolerance to cow milk at 6 and 12 months was similar in the two groups.

The foregoing studies show inconsistent findings on the usefulness of probiotics in the prevention or the treatment of allergy, specifically AD, in children. The discrepancies may be related to multiple factors (Table 2).

CONCLUSIONS

Food sIgE measurement is a useful screening test, particularly when skin-prick testing can not be done. Several factors should be considered in interpreting sIgE level. Predictive values derived from data on a certain group of patients may not be applicable to another group, particularly when a different assay method was used. Definitive decisions on individual cases should be based on appropriately designed challenge testing.

APT with foods may provide positive results that may or may not be clinically relevant. It seems to have a potential application in evaluation of EE. Standardization of the test material and interpretation is lacking at present.

EE does not seem to be a new disease. Its increasing diagnosis seems to be due to a higher awareness and better evaluation. Food allergy seems to be the cause in most, but not in all patients.

The usefulness of probiotics in allergy practice still is not clear, neither for prevention nor treatment. More studies are needed to identify the efficacious type, effective dose, timing to begin treatment, and duration.

ACKNOWLEDGMENTS

The author thanks Amanda Hammad for her excellent assistance in literature search and preparation of the article.

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