Editorial
Allergy Asthma Immunol Res. 2015 July;7(4):309-311.
http://dx.doi.org/10.4168/aair.2015.7.4.309
pISSN 2092-7355 • eISSN 2092-7363

AAIR
Allergy, Asthma & Immunology Research

# Diagnostic Decision Points of Specific IgE Titers in Patients With Food Allergy: Are They Appropriate in All Clinical Settings?

Tae Won Song

*Department of Pediatrics, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea*



In daily clinical practice, it is not so easy to make a confirmative diagnosis of food allergy. Interpretation of skin prick test and serum food-specific IgE (sIgE) test results is influenced by detailed clinical history of an individual patient, but ingested foods which provoke adverse reactions often contain many ingredients and lead to a misdiagnosis of food allergy. Oral food challenge is recommended for the diagnosis of food allergy, but we cannot always perform oral food challenge for various reasons, including recent severe reactions to food, severe atopic dermatitis, patient' and/or parents' refusal and noncooperation of young patients. Thus, from the physician's point of view, cut-off values of sIgE titers that provide high positive and negative predictive values would be very useful in clinical settings because they help determine which patient is more likely to have symptoms in response to a certain food and which are probably nonreactive.

Since Sampson[1,2] was first to publish studies on the efficacy of serum specific IgE in determining which food-allergic patient is more likely to fail oral food challenge,[3] their diagnostic decision points (DDPs) have been widely used in clinical practice worldwide as well as in Korea.[4] Positive predictive value (PPV) represents the proportion of symptomatic individuals to those with positive test results.[5] Positive predictive accuracy can be calculated by the following equation:

$$\text{Positive predictive accuracy} = sP / sP + (1 - f)(1 - P)$$

where s=sensitivity, f=specificity, and *P*=prevalence of the condition in the population studied.[2] The composition of the population investigated affects the positive predictive accuracy as denoted in the formula. Predictive accuracy is difficult to establish because it varies with the prevalence of disease.[2] Sampson *et al.*[2] attempted to minimize the influence of disease prevalence on DDPs among different populations and established DDPs from 90% specificity as an alternative approach. However, the value of the PPV was very low (50.0% in children <24 months of age and 59.3% in those ≥24 months of age, respectively) when the previously established DDPs of egg white-sIgE concentrations for egg allergy were applied in that study population; the value of the PPV was slightly lower than 95% (83.3% in children <24 months of age and 91.7% in those ≥24 months of age, respectively) when the previously established DDPs of cow milk-sIgE concentrations for milk allergy was applied in this study population.[6] Similar results have been reported in a recent study of Korean children demonstrating that the sensitivity and specificity of the previously established DDPs for egg white-sIgE are low.[7]

In the current issue of the *Allergy, Asthma & Immunology Research*, Kim *et al.*[6] suggest that it is more practical to use higher DDPs of egg white- and cow's milk-sIgE antibodies in Korean children for the diagnosis of egg and cow milk allergies in order to avoid unnecessary diet restriction. Predictive values vary from study to study (Tables 1 and 2).[1-3,5,6,8-15] These discrepancies may be due to various factors, such as patient age, duration of food allergen avoidance at the time of testing, patient selection, and clinical disorders of patients studied[8] as well as the prevalence of disease. DDPs with 95% predictive value are subjected to some limitations: (1) the majority of subjects with atopic dermatitis and elevated total IgE levels showed potentially skewed data and (2) many subjects with higher IgE antibodies to milk or egg did not undergo oral food challenge to confirm the clinical reactivity, thus limiting their diagnostic efficacy.[16]

When determining timing for reintroduction of egg or cow milk to patients who are likely to pass food challenge, physi-

**Correspondence to:** Tae Won Song, MD, PhD, Department of Pediatrics, Ilsan Paik Hospital, Inje University College of Medicine, 170 Juwharo, Ilsan-seogu, Goyang 411-706, Korea.
Tel: +82-31-910-7101; Fax: +82-31-910-7108; E-mail: twsong@paik.ac.kr
Received: April 17, 2015; Accepted: April 18, 2015
• There are no financial or other issues that might lead to conflict of interest.

**Table 1.** Positive predictive values of egg white-specific IgE titers reported from various studies

| Year | Reporter | Country | Number | Prevalence (%) | % of AD | PPV | Age | sIgE titer ($kU_A/L$) |
|---|---|---|---|---|---|---|---|---|
| 1997 | Sampson[1] | US | 126 | 73 | All | 95% PPV | 0.6-17.9 yr | 6 |
| **2001** | **Sampson[2]** | **US** | **75** | **80** | **61** | **90% specificity (95% PPV)** | **3 mo-14 yr** | **7*** |
| 2001 | Boyano-Martinez[9] | Spain | 81 | 79 | 43 | 94% PPV | <2 yr | 0.35 |
| 2001 | Roehr[10] | Germany | 98 | 24 | all | 100% PPV (with APT) | 2 mo-11.2 yr | 17.5 |
| **2002** | **Boyano-Martinez[11]** | **Spain** | **58** | **64** | **50** | **50th percentile of the frequency distribution** | **11-24 mo** | **1.98*** |
| 2003 | Osterballe[12] | Denmark | 56 | 64 | all | 95% PPV | <2 yr<br>>2 yr | 1.5<br>1.3 |
| 2005 | Celik-Bilgili[5] | Germany | 227 | 67 | 88 | 95% PPV | <1 yr<br>≥1 yr | 10.9<br>13.2 |
| 2007 | Komata[3] | Japan | 764 | 45 | 74 | 95% PPV | <1 yr<br>1 yr<br>≥2 yr | 13.0<br>23.0<br>30.0 |
| 2008 | Ando[13] | Japan | 108 | 62 | 94 | 95% PPV | 14 mo-13 yr | 7.4<br>(Heated; 30.7) |
| 2015 | Kim[6] | Korea | 273 | 19 | 81.3 | 95% PPV | <2 yr<br>≥2 yr | 22.9<br>28.1 |

*The most widely used PPV.
AD, atopic dermatitis; PPV, positive predictive value; sIgE, specific IgE; mo, months; yr, year.

**Table 2.** Positive predictive values of cow milk-specific IgE titers reported from various studies

| Year | Reporter | Country | Number | Prevalence (%) | % of AD | PPV | Age | sIgE titer ($kU_A/L$) |
|---|---|---|---|---|---|---|---|---|
| 1997 | Sampson[1] | US | 109 | 50 | All | 95% PPV | 0.6-17.9 yr | 32 |
| **2001** | **Sampson[2]** | **US** | **62** | **66** | **61** | **90% specificity (95% PPV)** | **3 mo-14 yr** | **15*** |
| **2001** | **Garcia-Ara[14]** | **Spain** | **170** | **44** | **23** | 90% PPV<br>**95% PPV** | <1 yr<br>**<1 yr** | 2.5<br>**5*** |
| 2001 | Roehr[10] | Germany | 98 | 41 | all | 100% PPV (with APT) | 2 mo-11.2 yr | 0.35 |
| 2004 | Garcia-Ara[15] | Spain | 66 | all | unrevealed | 90% PPV | 13-18 mo<br>19-24 mo<br>25-36 mo | 1.5<br>6<br>14 |
| 2005 | Celik-Bilgili[5] | Germany | 397 | 49 | 88 | 90% PPV | <1 yr<br>1-16.1 yr | 25.8<br>88.8 |
| 2007 | Komata[14] | Japan | 861 | 25 | 74 | 95% PPV | <1 yr<br>1 yr<br>≥2 yr | 5.8<br>38.6<br>57.3 |
| 2015 | Kim[6] | Korea | 225 | 23.1 | 81.3 | 90% PPV | <2 yr<br>≥2 yr | 31.4<br>10.1 |

*The most widely used PPV.
AD, atopic dermatitis; PPV, positive predictive value; sIgE, specific IgE; mo, month; yr, year.

cians should consider patient age, natural history of concerned food allergy, severity of previous symptoms, and reduction in the food-sIgE level in an individual patient.[4] Challenge tests can be performed in children when their food-sIgE level decreases to about one-fourth of the diagnostic decision point, unless they have experienced any recent allergic reaction.[2] Ando *et al.*[13] have reported that negative predictive value (NPV 84%), based on 95% sensitivity, is 0.6 $kU_A/L$ for egg white. Kim *et al.*[6] have suggested a new NPV for Korean children with suspected egg or milk allergy.[6] They reported that egg white -sIgE levels of


Allergy Asthma Immunol Res. 2015 July;7(4):309-311. http://dx.doi.org/10.4168/aair.2015.7.4.309

3.45 $kU_A$/L yield a NPV of 93.6% in children <24 months of age, while a NPV of 1.80 $kU_A$/L yield a NPV of 99.2% in those ≥24 months of age. The cow's milk-sIgE levels of 0.59 $kU_A$/L and 0.94 $kU_A$/L showed NPVs of 100% and 96.9%, respectively, in children <24 months of age and in those ≥24 months of age. These NPVs could provide data for clinicians to select patients who are likely to pass food challenge.

The accuracy of diagnostic tests in food allergy is important because a misdiagnosis of food allergy can lead to serious consequences, including nutritional deficiency.[16] The diagnosis of food allergy begins with detailed clinical history taking and thorough physical examination. Both skin prick tests and sIgE measurement alone are not sufficient to diagnose food allergy and should then be guided by the information gathered from the history. The double-blind placebo-controlled food challenge is still the gold standard for diagnosis of food allergy. However, predictive DDPs of sIgE levels could be useful for eliminating the need for unnecessary oral food challenges. Although the universal DDPs are in wide use, alternative DDPs of sIgE levels may improve the diagnostic accuracy in food allergy due to differences in clinical and demographical features of patients among countries or races.

## REFERENCES


1. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol 1997;100:444-51.
2. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;107:891-6.
3. Komata T, Söderström L, Borres MP, Tachimoto H, Ebisawa M. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. J Allergy Clin Immunol 2007;119:1272-4.
4. Song TW, Kim KW, Kim WK, Kim JH, Kim HH, Park YM, et al. Guidelines for the oral food challenges in children. Pediatr Allergy Respir Dis 2012;22:4-20.
5. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. Clin Exp Allergy 2005;35:268-73.
6. Kim J, Kim HY, Park MR, Choi J, Shim JY, Kim MJ, et al. Diagnostic decision points of specific IgE concentrations in Korean children with egg and cow's milk allergies. Allergy Asthma Immunol Res. 2015;7:332-8.
7. Min TK, Jeon YH, Yang HJ, Pyun BY. The clinical usefulness of IgE antibodies against egg white and its components in Korean children. Allergy Asthma Immunol Res 2013;5:138-42.
8. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol 2010;126:S1-58.
9. Boyano Martínez T, García-Ara C, Díaz-Pena JM, Muñoz FM, Garcia Sanchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. Clin Exp Allergy 2001;31:1464-9.
10. Roehr CC, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. J Allergy Clin Immunol 2001;107:548-53.
11. Boyano-Martínez T, García-Ara C, Díaz-Pena JM, Martín-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. J Allergy Clin Immunol 2002;110:304-9.
12. Osterballe M, Bindslev-Jensen C. Threshold levels in food challenge and specific IgE in patients with egg allergy: is there a relationship? J Allergy Clin Immunol 2003;112:196-201.
13. Ando H, Movérare R, Kondo Y, Tsuge I, Tanaka A, Borres MP, et al. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. J Allergy Clin Immunol 2008;122:583-8.
14. García-Ara C, Boyano-Martínez T, Díaz-Pena JM, Martín-Muñoz F, Reche-Frutos M, Martín-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. J Allergy Clin Immunol 2001;107:185-90.
15. García-Ara MC, Boyano-Martínez MT, Díaz-Pena JM, Martín-Muñoz MF, Martín-Esteban M. Cow's milk-specific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants. Clin Exp Allergy 2004;34:866-70.
16. Fleischer DM, Burks AW. Pitfalls in food allergy diagnosis: serum IgE testing. J Pediatr 2015;166:8-10.