

The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges

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Summary

Background Specific serum IgE is considered as one of the important diagnostic measures in the diagnostic work-up of food allergy.

Objective To evaluate the role of specific serum IgE in predicting the outcome of oral food challenges, and to determine threshold concentrations of specific serum IgE that could render double-blind, placebo-controlled food challenges unnecessary.

Methods In 501 children (median age 13 months), 992 controlled oral challenges were performed with cow's milk (CM), hen's egg (HE), wheat and soy. 440/501 (88%) children suffered from atopic dermatitis. For all children, specific IgE concentrations in serum were determined. Sensitivity, specificity, positive and negative predictive values, receiver operator characteristics-curves as well as predictive decision points were calculated.

Results Four hundred and forty-five out of 992 oral food challenges with allergens were assessed as positive. Sensitivity of specific serum IgE was 97% for HE, 83% for CM, 69% for soy, and 79% for wheat. Specificity was 51% for HE, 53% for CM, 50% for soy, and 38% for wheat. Calculating 90%, 95% and 99% predicted probabilities using logistic regression revealed predictive decision points of 6.3, 12.6, and 59.2 kU/L for HE, respectively. Subdividing our children in those of below or above 1 year of age resulted in a markedly different predicted probability for HE. For CM, only the 90% predicted probability (88.8 kU/L) could be calculated. No decision points could be determined for CM, wheat and soy.

Conclusion In general, specific serum IgE levels showed a correlation with the outcome of positive oral food challenges for CM and HE. Meaningful predictive decision points can be calculated for HE, which may help to avoid oral food challenges in some cases. However, data need to be ascertained for each allergen separately. Furthermore, the age of the patient population under investigation must also be taken into account.

Keywords atopy patch test, children, DBPCFC, food allergy, food challenge, skin prick test, specific IgE

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Introduction

An increase in the prevalence of food allergy has been reported recently [1, 2], especially for peanut [3]. Food allergy has an important impact on children's health and the most common foods in childhood are cow's milk (CM), hen's egg (HE), wheat and soy [4].

The diagnostic work-up of food allergy includes skin prick tests, atopy patch tests (APTs), and determination of specific IgE antibodies in serum. Double-blind, placebo-controlled food challenges (DBPCFC) are still generally accepted as the gold standard [5, 6]. However, oral food challenges are time consuming, costly, and can induce potentially severe clinical

symptoms. It would therefore be desirable to have non-invasive measures at hand that could render oral food challenges unnecessary.

In the literature, there are few studies investigating the role of specific serum IgE levels for the outcome of oral food challenges [7–11]. The aim of this study was therefore to evaluate retrospectively the predictive value of serum specific IgE concentrations in a large number of children who underwent oral food challenges with CM, HE, wheat and soy.

Materials and methods

Population

We studied 501 children admitted consecutively to our ward. The only inclusion criterion was suspicion of food-related symptoms by parents or physicians. Ages ranged from 1

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month to 16.1 years (median 13 months), with 298 boys (60%) and 203 girls (40%). Four hundred and forty out of 501 (88%) suffered from atopic dermatitis (AD) as defined by the criteria of Sampson [12] and Seymour [13], modified from Hanifin and Rajka [14]. Two hundred and four children had mild AD (severity scoring of atopic dermatitis (SCORAD) ≤ 25 points), 116 moderate AD (25–50 points) and 56 severe AD (≥ 50 points). Sixty-four children had no clinical symptoms of AD at the time of the oral challenge. Nine hundred and ninety-two oral allergen provocations were performed in the 501 children.

Scoring of atopic dermatitis

Severity of eczema was scored according to the SCORAD score [15], with assessment of 'topography' items (affected skin area), 'intensity' criteria (extent of erythema, oedema, crusts, excoriations, lichenification, xerosis) and subjective or reported parameters (extent of itch and loss of sleep). The maximum possible score was 103 points.

Determination of specific immunoglobulin E antibodies

Blood was drawn prior to the oral challenge. Patient sera were analysed for concentrations of specific IgE antibody titres to CM, HE, wheat and soy, determined by fluorescence enzyme immunoassay using the Pharmacia CAP-system[®] (Pharmacia Diagnostics, Uppsala, Sweden) [16]. The detection limit of the CAP-system was 0.35 kU/L IgE; children were regarded as sensitized if specific IgE was higher.

Oral food challenges

Oral challenges were performed in all children using the four most common food allergens in our population (CM, HE, wheat and soy), and placebo. Children on an antihistamine

were advised to avoid it for 72 h prior to provocation. Topical glucocorticosteroids were allowed twice daily at a concentration of 1% hydrocortisone or 0.01% betamethasone.

A total of 992 controlled oral food challenges were performed: 728 challenges were carried out in a double-blind, placebo-controlled manner [17], and 264 challenges in an open manner. Open challenges were allowed if children were younger than 1 year and had a history of immediate type reactions; in other cases challenges were performed as DBPCFC. In more detail, 398/992 (40%) challenges were performed with CM, 227/992 (23%) with HE, 178/992 (18%) with wheat and 189/992 (19%) with soy.

Usually, blocks of two allergens and one placebo are administered. The clinical dietician performed randomization and preparation of the challenges. Briefly, every 48 h successive doses of fresh pasteurized CM containing 3.5% fat, of fresh whisked HE, of soy milk, and of wheat powder (Kröner, Ibbenbüren, Germany) (total amount of 5 g of wheat protein) or placebo (Neocate[®], SHS, Liverpool, UK) were administered (Table 1). All open challenges were performed using the identical titration steps as the double-blind ones. The time interval between doses was 20 min. Full emergency equipment was at hand.

The provocation was stopped if clinical symptoms were observed or the highest dose was reached. The children were observed for 48 h after each challenge on an in-patient basis in order to detect late clinical reactions. The food challenges were scored as positive by a paediatric allergy specialist if one or more of the following objective clinical reactions were noted: urticaria, angio-oedema, wheezing, vomiting, diarrhoea, abdominal pain, shock or exacerbation of eczema (at least 10 points increase in SCORAD score). Early reactions were defined as clinical symptoms within 120 min after administering the highest dose, late reactions as symptoms occurring after 2 h.

Table 1. Volumes and amounts of protein used for oral food challenges

Food	Challenge step	1	2	3	4	5	6	7	Total
CM	Volume CM (mL)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Volume BS (mL)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Total volume (mL)	0.2	0.6	2.0	6.0	20.0	60.0	200.0	288.8
	Protein (g)	0.003	0.01	0.033	0.1	0.33	1.0	3.3	4.8
HE	Volume HE (mL)	0.04	0.11	0.38	1.14	3.8	11.4	38.0	54.9
	Volume BS (mL)	0.16	0.49	1.62	4.86	16.2	48.6	162.0	233.9
	Total volume (mL)	0.2	0.6	2.0	6.0	20.0	60.0	200.0	288.8
	Protein (g)	0.005	0.014	0.05	0.14	0.46	1.4	4.6	6.2
Wheat	Volume wheat (mL)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Volume BS (mL)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Total volume (mL)	0.2	0.6	1.2	6.0	20.0	60.0	200.0	288.8
	Protein (g)	0.003	0.008	0.028	0.083	0.28	0.83	2.8	4.0
Soy	Volume soy (mL)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Volume BS (mL)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Total volume (mL)	0.2	0.6	2.0	6.0	20.0	60.0	200.0	288.8
	Protein (g)	0.004	0.011	0.04	0.11	0.36	1.1	3.6	5.2

CM, fresh native cow's milk; HE, fresh native whisked hen's egg; wheat, wheat powder (5 g/144.4 mL = 4 g wheat protein); soy, fresh native soy milk; BS, base solution (amino acid formula).

Statistical analyses

For the statistical analyses we used SPSS for Windows (version 10.0, SPSS, Chicago, IL, USA). Two by two tables were used to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and efficiency. The outcomes of tests were analysed in detail (early, late and combined phase reactions). Test sensitivity was defined as the proportion of true positives detected, specificity as the proportion of true negatives detected. The PPV describes the proportion of symptomatic individuals among test positives, and the NPV the proportion of non-symptomatic individuals among test negatives. To calculate probabilities of the outcome of oral food challenges by means of specific IgE in serum we used the logistic regression with following formula, where x is defined as $\ln(kU/L)$ [8]:

$$P = \frac{1}{e^{-\alpha - \beta x} + 1}$$

Results

Clinical outcome of challenges

We analysed a total of 992 controlled oral challenges with CM, HE, wheat and soy in 501 children. Four hundred and forty-five out of 992 (45%) of verum challenges, and 10/354 (3%) of placebo challenges were assessed as positive. Sixty-seven percent of the egg challenges were assessed as positive, 49% of those with milk, 35% of those with wheat and 19% of those with soy. The clinical manifestations during oral food

challenges are shown in Fig. 1. Two hundred and ninety-eight out of 445 (67%) of positive challenges lead to early phase reactions, 63/445 (14%) to late phase reactions, and 84/445 (19%) to combined early and late reactions.

Allergological tests and outcome of oral food challenges

The results for sensitivity, specificity, PPVs, NPVs and efficiency are shown in Table 2. While sensitivity values were between 69% and 97%, specificity values were between 38% and 53%.

Sensitivity and specificity are dependent on the cut-off points selected. Graphic representation of sensitivity and specificity at various operating points can be obtained by calculating receiver operator characteristics (ROC-curves). They revealed that CM (area under the curve (AUC) 0.76) and HE (AUC 0.88) showed acceptable values, while for wheat (AUC 0.66) and soy (AUC 0.64) the relationship between sensitivity and specificity was not satisfying (data not shown). Figure 2 shows that there is a tendency towards a relationship between specific IgE values (expressed as CAP classes) and percentages of positive oral food challenges. In the case of CM and HE, challenges were positive from CAP class 5 on (>50.0 kU/L). For wheat and soy there was no such clear relationship between specific IgE levels and the probability of positive food challenges.

Using the logistic regression model proposed by Sampson allows calculation of predicted probabilities for showing a positive oral food challenge at a given specific IgE value. For example, choosing a 95% predicted probability resulted in a predictive decision point of 12.6 kU/L for HE (Fig. 3) [8].

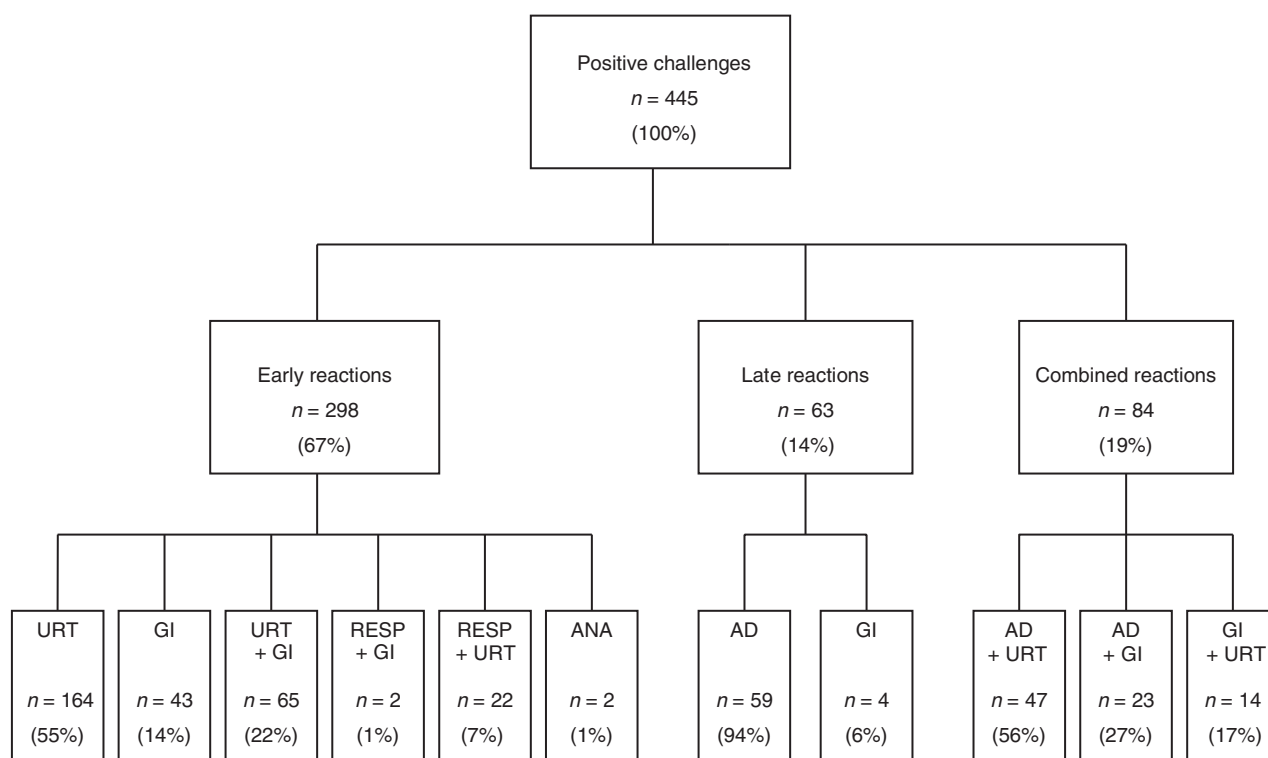


Fig. 1. Clinical reactions during oral food challenges. URT, urticaria; GI, gastro-intestinal; RESP, respiratory; ANA, severe systemic reactions; AD, worsening of eczema.

This criterion was fulfilled by 48/151 positive challenges with HE (32%). Calculating 99% predicted probability resulted in a cut-off point of 59.2 kU/L for HE, which was fulfilled by 7/151 positive challenges (5%) with HE. For CM, only the 90% predicted probability (88.8 kU/L) could be calculated. No 90%, 95% or 99% predicted probabilities could be determined for wheat and soy.

Subdividing our children in those of below or above 1 year of age provided different predicted probabilities for HE (Table 3). In children less than 1 year, the decision point using a 95% predicted probability was 10.9 kU/L, while it was 13.2 kU/L for children over 1 year of age. Choosing a 99% predicted probability, this difference was 88.6 and 58.2 kU/L, respectively.

Table 2. Predictive capacity of specific IgE for oral food challenges

	CM (%)	HE (%)	Wheat (%)	Soy (%)
Sensitivity	83	97	79	69
Specificity	53	51	38	50
PPV	63	80	41	22
NPV	76	89	77	88
Efficiency	68	81	53	53

CM, cow's milk; HE, hen's egg; PPV, positive predictive value; NPV, negative predictive value. Cross tables were calculated on the basis of positive or negative oral food challenges and specific serum IgE concentrations above or below detection limit (0.35 kU/L).

Discussion

Our data results that specific IgE levels in serum show a correlation with the outcome of positive oral food challenges for some allergens. Calculating predictive decision points may help to facilitate the diagnostic work-up of food allergy. However, data need to be ascertained for each allergen separately.

Our analysis was retrospective. This does not seem to represent a major bias, since it has been shown that retrospectively calculated decision points are comparable with those prospectively investigated [8]. Sensitivity, specificity, PPV and NPV were calculated for 445 positive and 547 negative oral verum challenges. Our findings seem valid since there were only 10/354 (3%) positive placebo reactions during DBPCFC in this series, although late phase reactions were also included in the clinical judgment of oral food challenges, which are more difficult to assess. In our study, 88% of the population suffered from AD. We carefully described the clinical symptoms of our population during oral food challenges (Fig. 1), since results may be dependent on the population studied.

In our population, 40% of oral food challenges were performed with CM, and 23% with HE, while the figures for wheat and soy were 18% and 19%, respectively. HE showed the highest percentage of positive reactions (67%), followed by CM with 49%. This is in accordance with the literature, which reports 70% and 43%, respectively [18]. Interestingly,

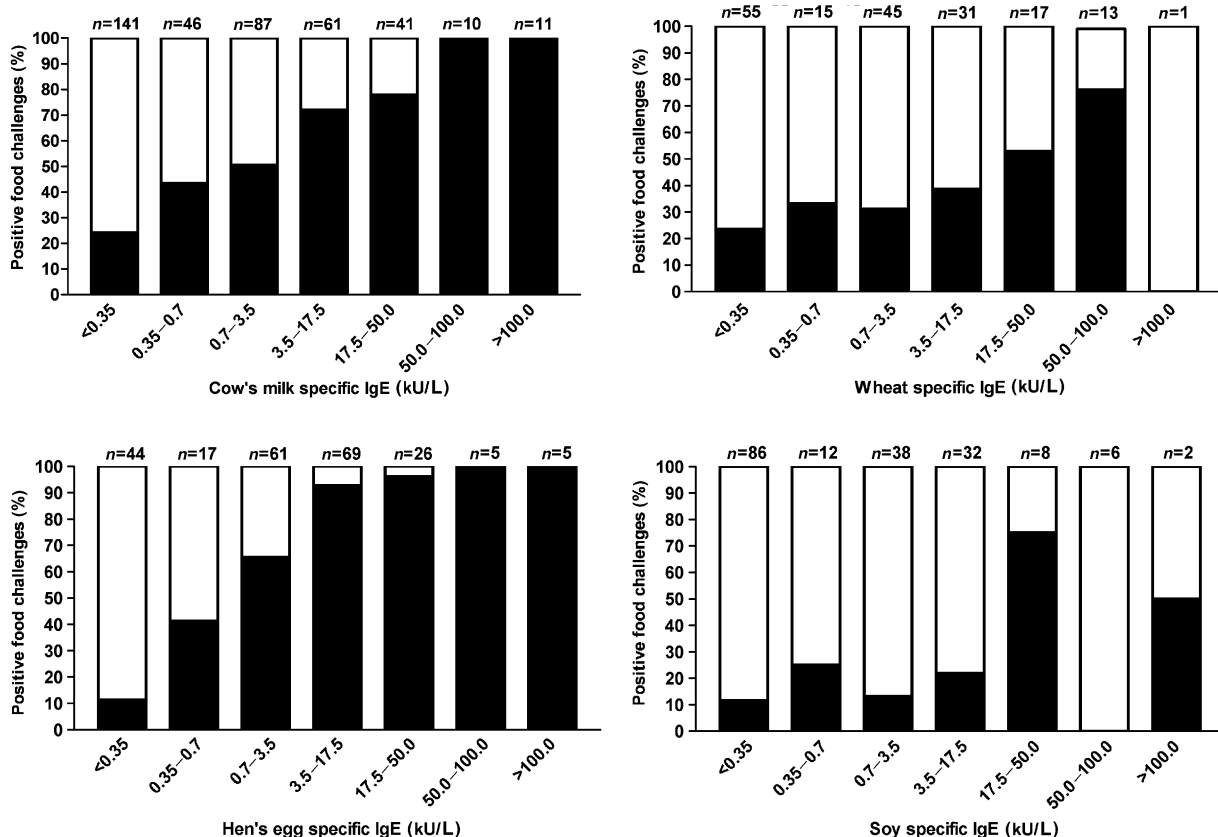


Fig. 2. Specific IgE in relationship to the outcome of oral food challenges.

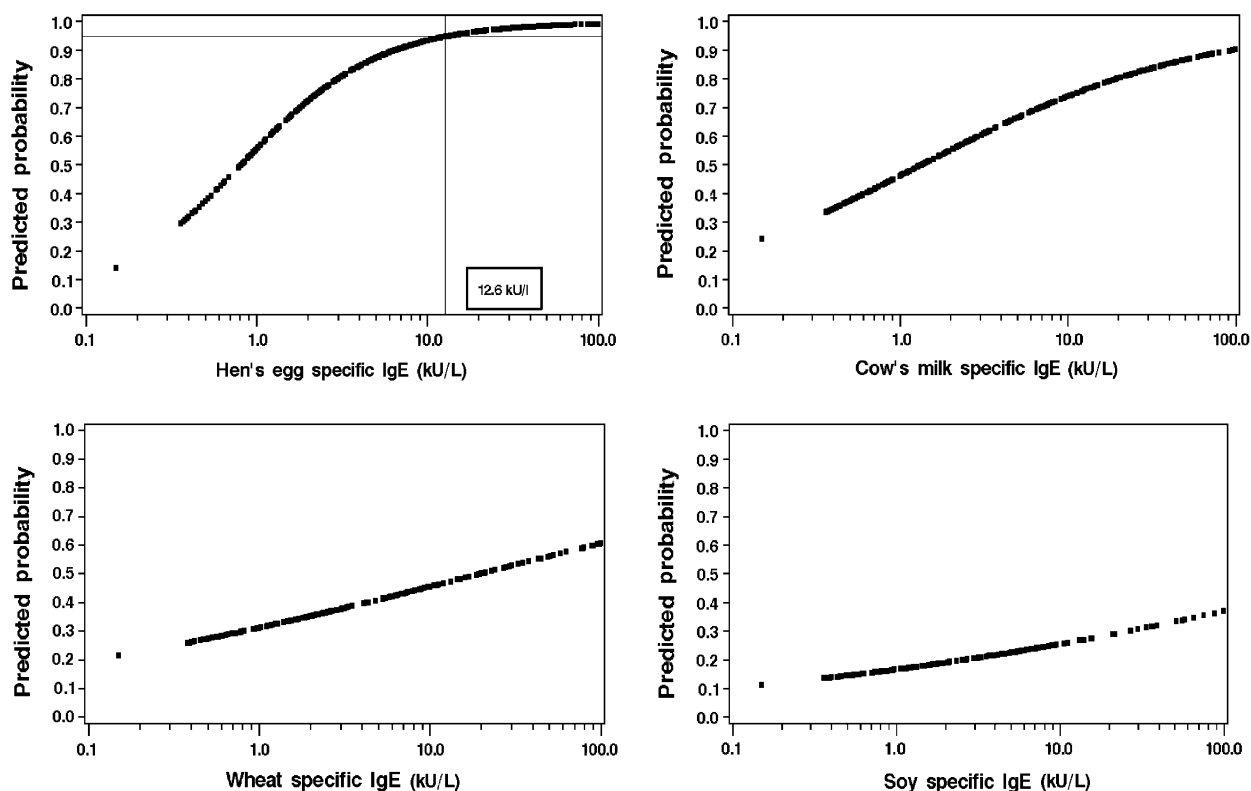


Fig. 3. Predicted probabilities of showing a positive oral food challenge at a given specific IgE value. Thin lines and inset numbers represent 95% predicted probabilities.

Table 3. Predicted probabilities (90%, 95% and 99%) for children below ($n = 206$) and above ($n = 295$) 1 year of age

Cut-off (%)	< 1 year	≥ 1 year	All children
CM			
90	25.8 kU/L	*	88.8 kU/L
95	*	*	*
99	*	*	*
	($n = 186$)	($n = 212$)	($n = 398$)
HE			
90	4.2 kU/L	6.7 kU/L	6.3 kU/L
95	10.9 kU/L	13.2 kU/L	12.6 kU/L
99	88.6 kU/L	58.2 kU/L	59.2 kU/L
	($n = 41$)	($n = 186$)	($n = 227$)
Wheat			
90	*	*	*
95	*	*	*
99	*	*	*
	($n = 75$)	($n = 102$)	($n = 177$)
Soy			
90	*	*	*
95	*	*	*
99	*	*	*
	($n = 81$)	($n = 103$)	($n = 184$)

*90%, 95% and/or 99% predictive values could not be calculated.
CM, cow's milk; HE, hen's egg.

CM and HE showed predominantly clinical reactions of an early type, which have also been reported in a recent study investigating the role of non-IgE-mediated oral food challenges [19].

Calculating the predictive capacity of specific IgE concentrations to the four foods resulted in acceptable sensitivity numbers of 69–97%, while the values for specificity were between 38% and 53% (Table 2). Best values were found for HE. However, sensitivity and specificity values of 100% can be obtained if the APT is used in combination with specific IgE concentrations [20]. It could be shown that if both diagnostic measures were positive, oral food challenges can be avoided in some cases.

Simply plotting percentages of positive food challenges against the specific IgE values in CAP classes resulted in a dose–response relationship (Fig. 2), which was especially prominent for CM and HE. The effect was less marked in the other allergens, probably because of the relatively low number of provocations for some single CAP classes. This emphasizes the need for large study populations.

In our view, the curves calculated by linear regression first proposed by Sampson [8] provide the best information for clinical relevance. They make it possible both to provide the predicted probability (in %) for a given specific IgE value, as well as providing the required IgE level for a pre-chosen probability (Fig. 3). For HE, our 95% decision point (12.6 kU/L) was similar to that of Sampson (7 kU/L), confirming his results in a large number of children. However, for CM, no 95% or 99% predictive decision could be obtained in our children, while Sampson described a 95% predicted probability of 15 kU/L in his study [8]. A Spanish group found even 5 kU/L as a PPV of 95%, investigating the role of specific IgE in infants with immediate reactions during a CM challenge [9]. From our data, there is no explanation for these differences in CM compared with HE.

These differences in the decision points may be the result of different ages of the populations studied: while Sampson's [8] children showed a median age of 3.8 years, our children had a median age of 13 months, and the Spanish group of even 4.8 months [9]. In our study, subdividing children in those of below and above 1 year of age resulted in a markedly different predicted probability for HE (Table 3). There was a tendency towards lower decision points in the infant age group. Furthermore, for CM, only in infants the 90% predicted probability could be calculated (25.8 kU/L).

In our view, 99% PPVs should be preferred over 95% ones to avoid unnecessary diets in one out of 20 children. The 99% cut-off predictive values of 59.2 kU/L for HE was fulfilled by 7/151 positive challenges with HE (5%). The numbers are quite low; however, one may argue that every single oral challenge, which may become superfluous by using the 99% predicted probabilities eliminates the risk of severe side effects in the children with the highest specific IgE levels and therefore the highest probability of developing severe side effects during oral challenges.

For wheat and soy, predictive probabilities did not exceed 61% and 37%, respectively, which limits the value of this parameter for these food allergens. These results clearly show, that decision points have to be studied for each food allergen separately. Furthermore, there does not seem to be a significant relationship between the quantification of specific IgE and the challenge threshold level [11].

In conclusion, specific serum IgE levels showed a correlation with the outcome of positive oral food challenges. Predictive decision points can be calculated, which may help to avoid oral food challenges in some cases. However, data need to be ascertained for each allergen separately, and the age of the patient population under investigation must also be taken into account.

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