

Letter to the Editor

Usefulness of specific IgE levels in predicting cow's milk allergy

To the Editor:

Food allergy affects as many as 6% to 8% of children in countries with a Western lifestyle. At least 1/3 of these children experience cow's milk allergy (CMA).¹ Double-blind, placebo-controlled food challenges (DBPCFCs) are the gold standard for diagnosing food allergy.^{1,2} When clinical history suggests CMA, this is not always confirmed by DBPCFC.³ An accurate diagnosis is essential, because overdiagnosis and underdiagnosis of food allergy has led to physical and psychosocial problems.⁴ However, a DBPCFC is time consuming and expensive, may be troublesome for the patient, and can cause severe systemic reactions.¹ A few studies investigated the relationship between specific IgE levels for cow's milk (CM) and the outcome of a DBPCFC.⁵⁻⁹ They showed that increasingly higher concentrations of CM specific IgE were associated with an increased likelihood of CMA, but the cutoff value separating those infants who have a high versus low probability of having a positive challenge result varied considerably between the different studies. However, these studies were not consistent with respect to the nature of the provocation tests (open or double-blind), to the protocol of provocation tests used, and to the focus on early and/or late reactions. The purpose of this study was to determine CM specific IgE cutoff values for 90% and 95% positive predictive value (PPV) for CMA by using only DBPCFC, continuing the food challenge until objective symptoms were present and focusing only on acute reactions.

We retrospectively studied the relationship between levels of CM specific IgE and the likelihood of a positive DBPCFC for CM in 213 Dutch children (134 boys, 79 girls) in our tertiary hospital. Their mean age was 2.97 years (0.23-15.49). Of these, 178 children (84%) had atopic dermatitis. All participants underwent a DBPCFC¹⁰ between 2001 and 2006. DBPCFC was performed in the day care unit of the hospital, where appropriate medication and resuscitation equipment were directly available. Every patient remained under observation after intake of the last provocation dose (2 hours in case of negative and 4 hours in case of positive DBPCFC result) before going home. Increasing doses of CM or placebo were given until objective signs of an acute allergic reaction (urticaria, angioedema, repetitive vomiting, dyspnea, wheezing, cyanosis, or cardiovascular symptoms) occurred or until the highest dose (90 mL, cumulative dose of 250 mL; 4.5 g CM protein) was reached. Serum samples from all patients were analyzed for specific IgE antibodies to CM by using the CAP system FEIA (Pharmacia Diagnostics, Uppsala, Sweden). CM specific IgE was measured within 3 months before the DBPCFC. To compare with other studies, both 2 by 2 tables and logistic regression analysis (using log sIgE)⁷ were used to calculate probabilities for the outcome of DBPCFC for different CM specific IgE levels.

Cow's milk allergy was confirmed by DBPCFC in 94 of 213 patients (44%). Calculating receiver operator characteristic curves revealed an area under the curve of 0.86, and 0.92 in children <2.5 years of age. The association between specific IgE levels and outcome of DBPCFC is represented in Fig 1. Cutoff values calculated by 2 methods are represented in Table I.

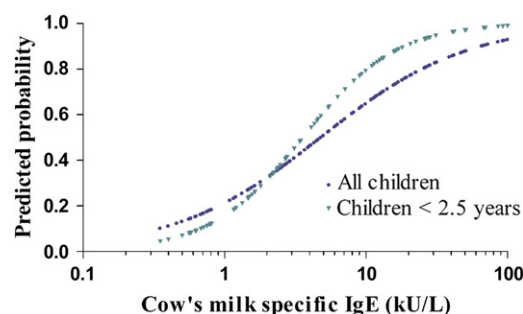


FIG 1. Probabilities of showing a positive DBPCFC result for cow's milk at a given cow's milk specific IgE level (using logistic regression analysis with ln sIgE).

TABLE I. Predicted probabilities (90%, 95%, and 99%/100%) of showing a positive CM challenge result in different age groups

Percent PPV	Cutoff level CM specific IgE (kU/L) (% of children with sIgE above this value)		
	All children (N = 213)	<1 y old (N = 46)	<2.5 y old (N = 142)
Using 2 by 2 tables			
90	26.8 (18.3)	†	5.0 (31.0)
95	52* (10.8)	†	7.5 (28.2)
100	94 (5.6)	23 (8.7)	23 (16.2)
Using logistic regression			
90	66.4 (10.3)	18.1 (13.0)	19.0 (17.6)
95	†	31.5 (8.7)	33.4 (11.3)
99	†	†	†

*Exact PPV by 52 kU/L was 95.7%.

†Specific IgE above 100 kU/L, clinically not relevant.

‡Group was too small to attain 90% and 95% PPVs.

Differences were found between 2-by-2 table analysis and logistic regression analysis. A subgroup analysis was performed for different age groups. Lower cutoff points were found for the children under 2.5 years of age, and all children in this group with a specific IgE ≥ 23 kU/L had a positive challenge result (100% PPV). No correlation was found between the level of CM specific IgE and the severity of the allergic reaction in either group (data not shown).

This study confirmed that increasingly higher concentrations of CM specific IgE were associated with an increasing likelihood of a positive DBPCFC result in children.⁵⁻⁹ Mainly for children <2.5 years of age, a strong association was found. Whereas other studies reported lower cutoff points for children <1 year of age,^{6,8} we found lower cutoff points for the group of children under 2.5 years of age. This is important because children <2.5 years of age account for the largest group of children with the suspicion of CMA, and most children become tolerant by the age of 3 years. Moreover, we found a 100% PPV for a CM specific IgE of >23 kU/L. In other studies, no 100% PPVs were reported. Our results were quite consistent with the results of Garcia-Ara et al.⁸ The differences in cutoff values for all children between our study and that performed by Sampson et al.^{5,7} are not easy to explain. First, these differences may be a result of a difference in study population. In our study, the prevalence of CMA is 44%, whereas in the

2 studies of Sampson et al,^{5,7} a prevalence of 49% and 66% was found. A second possible reason for the observed differences is differences in performance of the DBPCFC and especially criteria for a positive challenge result. In the study of Celik-Bilgili et al,⁶ higher cutoff values were found. However, they based the cutoff values on PPV calculated by logistic regression analysis, whereas other studies used 2-by-2 tables. Although logistic regression analysis and 2-by-2 tables should provide the same cutoff points, a higher cutoff value for CM specific IgE is found by using logistic regression with ln sIgE. This partly explains the differences in cutoff values between the different studies. Although logistic regression analysis has the advantage that the required IgE level for a prechosen probability (ie, 95% PPV) and the predicted probability for a given specific IgE can be calculated,⁶ both methods are reliable.

Establishing cutoff points is meant for saving specific groups from undergoing a DBPCFC. Using the 90%, 95%, and 100% PPV for all children in this tertiary population with a high prevalence of eczema would render a DBPCFC superfluous in 18%, 11%, and 5.6% of the children, respectively. However, applying the 90%, 95%, and 100% cutoff values to our population would even render a DBPCFC superfluous in 31%, 28%, and 16%, respectively, of children under 2.5 years of age. Whether to use the 90%, 95%, or 100% cutoff point in daily practice is left to the individual clinician.

This was a retrospective study. However, all children underwent a standardized DBPCFC within 3 months after CM specific IgE was determined, and the inclusion criteria were not changed during 2001 and 2006. Therefore we do not expect that a prospective study would yield other results.

We conclude that DBPCFCs still remain an important diagnostic tool in CMA, but specific IgE decision points can render controlled oral food challenges superfluous in some of the patients, especially in children under 2.5 years of age.

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