

with oral antihistamines and inhaled steroids were later initiated due to development of wheezing.

In summary, we report the first case of a pediatric patient with IgE-mediated allergy to glatiramer acetate, presenting with a severe systemic reaction, in whom a novel and successful desensitization protocol was applied that allowed her to resume the use of this medication. Furthermore, we have established a skin test protocol which can potentially be helpful in evaluating patients with suspected IgE-mediated reactions to glatiramer acetate. Our experience supports the notion that allergy evaluation and desensitization can be helpful in pediatric patients with a history of hypersensitivity

reactions to glatiramer acetate and may allow continuation of this extremely powerful therapeutic agent available for the treatment of MS.

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Can total IgE/specific IgE ratio predict tolerance in cow's milk allergic children?

To the Editor,

Cow's milk (CM) allergy is the most common food allergy in children. It affects 2–3% of them (1). Studies have shown that spontaneous development of tolerance would appear at third year of life, having worse prognosis in older children (1). The mechanism by which tolerance to CM is achieved is not clear but the immunologic participation of regulatory T cells; the increase of IgG4 and IgA has been described. Those patients, who remain allergic at 10, usually show high levels of CM-specific IgE having often a high risk of anaphylactic reactions with small amounts of CM proteins (1). The diagnosis of CM allergy is based on clinical history, positive skin prick test (SPT) and/or specific IgE, and a positive oral food challenge (OFC) (2). The OFC is the gold standard for diagnosing, but the decision to perform it is complex (3). Many factors including the possibility of severe systemic reactions, medical records, SPT, and specific IgE levels must be taken into account when deciding to carry out it. Variability criteria from when is the best time not only to perform a diagnostic OFC,

but also to reintroduce CM in usual diets, supports the necessity of finding a tool that could predict tolerance (1, 4–6). We should not forget that food allergy has serious and immediate consequences because of accidental exposure to CM, and dietary restrictions that may influence the nutritional and social life of the child.

Medical control for CM-allergic children includes regular practice of SPT and specific IgE to consider when spontaneous tolerance is developed or when is the best time for an OFC to be performed. It is not advisable to undergo a diagnostic OFC, in children under 1 year old if CM-specific IgE ≥ 2.5 KU/l because of its high positive predictive value (90%) (5). Sampson (6) also refers a positive predictive value of 95%, in children with a median age of 3.8 years and CM-specific IgE ≥ 15 KU/l. In our experience, if we consider the current cutoff points for CM-specific IgE and casein-specific IgE from which is not advisable to make an OFC, it is possible that we leave with unnecessary avoidance of diet for some tolerant patients (7, 8). In a previous study, 24% of the patients who

were proposed for oral immunotherapy (as the reference values did not suggest the possibility of tolerance at 5 years), tolerated when submitted to an OFC (8).

Specific IgE/total IgE ratio was used in other studies to predict food allergy and found no benefit in using it compared with specific IgE (3). Di Lorenzo et al. also used this ratio for predicting clinical response to specific immunotherapy. It is based on the hypothesis that a greater proportion of circulating specific IgE with respect to the total IgE means that specific IgE is bound to mast cells and basophils and thus there is a greater ability to implement an allergic response against the allergen. This is the most important mechanism involved in respiratory allergy in order to respond appropriately to allergen-specific immunotherapy (9). In clinical practice, we observe that between patients with similar values of specific IgE, those who have a higher total IgE more often tolerate. This usually happens with patients with atopic dermatitis (AD) that have higher total IgE levels as well as sensitization to food and respiratory allergens without clinical correlation (4). In this context, we sought to assess whether total IgE/CM-specific IgE (CM ratio) or total IgE/casein-specific IgE (casein ratio) can be more useful in predicting tolerance than the only measurement of specific IgE, and to determine the highest sensitivity cutoff points.

Medical records of 178 patients with suspected CM allergy were retrospectively reviewed. All the patients underwent an OFC, in the Pediatric Allergy and Clinical Immunology Section, Hospital Sant Joan de Déu, Barcelona, between January 2010 and December 2011. Children ranged in age at challenge time, from 5 months to 13 years, (median 3.4), mostly boys (n 94, 53%). Twenty-three percent had mild AD, 31% other food allergies, 10% asthma, and 53% had not personal atopic history. Inclusion criteria were as follows: having a positive clinical history of CM allergy, a positive SPT and/or positive specific IgE values. A total of 178 OFC were performed, regardless of specific IgE SPT values. Written informed consent was obtained. Outcome of the OFC was evaluated as tolerant or allergic. Clinical data of SPT, specific IgE and total IgE levels, at the time of the initial visit and at OFC were collected. Total IgE and specific IgE determinations were performed by the ImmunoCAP method (ThermoFisher Scientific), being the minimum value 0.35 KU/l. If values were >100 KU/l, a serum dilution was performed and the results were quantified. SPT were performed with standardized Leti

Lab. extracts (Barcelona, Spain), for CM (20 mg/ml), casein (10 mg/mL), α -lactalbumin (20 mg/ml), and β -lactoglobulin (20 mg/ml). One-millimeter lancets (Stallergenes Lab, Paris, France) were used, and the results were evaluated after 15 min using the Prick film® method by Immunotek Lab. (Madrid, Spain). The largest diameter of the wheal in mm was evaluated. Double-blind placebo-controlled food challenge described by the Pediatric Spanish Clinical Immunology and Allergy Society (10) was used in patients over 5 years old. Open challenge was performed in children younger than 5 years, at doses of 2, 5, 10, 25, 50, 100, and 150 ml with 1-h interval between doses (5, 10). If an anaphylactic reaction occurred, they were classified, according to European Academy of Allergy and Clinical Immunology position paper criteria (11).

Statistical study included the following: Mann–Whitney U -test to examine differences in data distributions between tolerant and allergic groups, receiver operating characteristic (ROC) curve were done for CM and casein ratios, and area under the curve (AUC) and its confidence interval and p value were analyzed to determine how well each ratio can distinguish between the tolerant and allergic patients. AUC were compared using the bootstrap method implemented in the pROC R package. Analyses were performed with SPSS 20. Results were considered statistically significant for $p < 0.05$.

At the initial visit, 79 children (44.4%) reported clinical history of anaphylaxis, 63 (35.4%) urticaria, and 12 (6.7%) gastrointestinal (GI) symptoms. There were missing data from clinical symptoms, SPT, and total IgE levels in seven children because they had been referred from other centers without information. At challenge time, mean CM-specific IgE was 19.1 KU/l (range: 0–727) and casein-specific IgE 19.7 KU/l (range: 0–867) (n 178). Mean SPT to CM was 8 mm and 5 mm for casein, missing data in 12 patients (n 166). Hundred and seven children (60%) tolerated CM, while 71 (40%) reacted: 49 children (69%) suffered anaphylaxis, 16 (22.5%) urticaria, and 6 (8.5%) GI symptoms. Regarding severity: 20.4% anaphylaxis grade 1, 8.2% grade 2, 32.6% grade 3, and 38.8% grade 4 according to Sampson's criteria (12). Median CM-specific IgE, casein-specific IgE, SPT, CM ratio, and casein ratio at OFC were compared in tolerant and allergic children, showing statistical significant differences between the two groups. (Table 1).

Receiver operating characteristic curves were performed to assess how total IgE, CM-specific IgE, and casein-specific IgE

Table 1 Characteristics of median total IgE, specific IgE, SPT, and ratios between tolerant and allergic children

	Tolerant	Allergic	p Value
Total IgE (KU/l)	349.33 (2–4239)	287.97 (4–1951)	0.458
CM-specific IgE (KU/l)	3.41 (0–37.1)	42.47 (0.1–727)	<0.001
Casein-specific IgE (KU/l)	1.48 (0.01–26.7)	47.18 (0–867)	<0.001
CM SPT (mm)	6.86 (0–19)	9.77 (0–21)	<0.001
Casein SPT (mm)	4.01 (0–15)	6.92 (0–21)	<0.001
Total IgE/casein-specific IgE	293.92 (4.28–4566.67)	46.19 (1.21–7124)	<0.001
Total IgE/CM-specific IgE	110.48 (3.72–1065.6)	16.67 (1.49–2872.58)	<0.001

CM, Cow's milk; SPT, skin prick test.

can predict tolerance (Fig. 1). The AUC for total IgE was 0.53 (CI 95% 0.45–0.62), for casein-specific IgE 0.72 (CI 95% 0.64–0.80), and for CM-specific IgE 0.71 (CI 95% 0.63–0.79). The AUC was 0.76 (CI 95% 0.67–0.83) for casein ratio, and 0.75 (CI 95% 0.67–0.82) for CM ratio, both with $p < 0.001$ (Fig 2). The highest sensitivity cutoff point was determined for the ratios: CM ratio ≥ 3.75 and casein ratio ≥ 4.33 , 99% sensitivity and 20% specificity. When giving equal weight to sensitivity and specificity, the optimal cutoff point was CM ratio ≥ 45.65 and casein ratio ≥ 123.90 . Comparison between CM-specific IgE, casein-specific IgE, CM ratio, and casein ratio ROC curves reported no statistical significance.

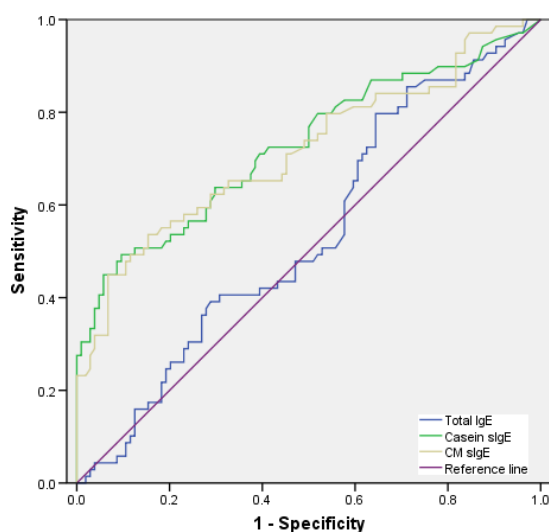


Figure 1 Total IgE/casein-specific IgE and total IgE/Cow's milk (CM)-specific IgE ratios predicting tolerance.

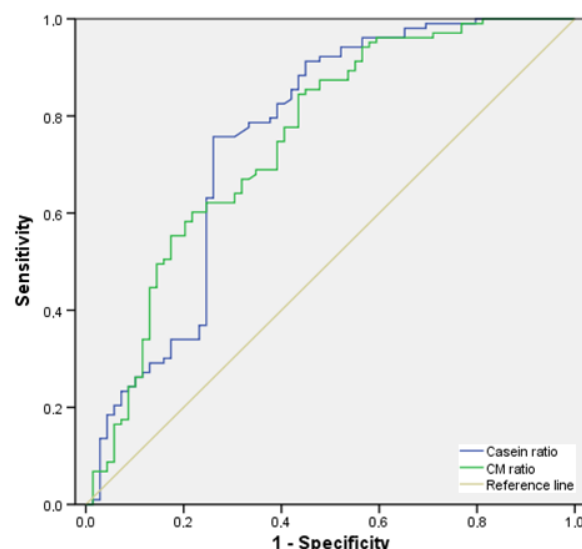


Figure 2 Characteristics of median total IgE, specific IgE, skin prick test and ratios between tolerant and allergic children.

Firstly, we bring out that our children have a high percentage of anaphylaxis, not only at the initial visit (44.4%, $n = 178$), but also after OFC (69%, $n = 71$). Noteworthy, only 9.5% of our children presented mild AD-like symptom of CM allergy, but this symptom was not reproduced at OFC. Other series refer 60% of children with AD. At the initial visit, almost half of the patients (44.3%) presented with clinical history of low severity (grade 1) anaphylaxis, but at OFC, 71.4% had grade 3 and 4 anaphylaxis. This clearly correlates with high mean levels of specific IgE (CM-specific IgE 42.47 KU/l, casein-specific IgE 47.18 KU/l).

The review of these 178 patients confirms that both CM-specific IgE and casein-specific IgE are good markers in predicting tolerance, and that there are statistically significant differences between the two groups, tolerant and allergic children (Fig. 1). The average CM-specific IgE is 3.41 KU/l and casein-specific IgE is 1.48 KU/l in tolerant patients and 42.47 and 47.18 KU/l in allergics, respectively, with statistically significant differences (Table 1). Regarding cutoff points for ratios, we choose the highest sensitive value which more likely detects tolerant patients (CM ratio ≥ 3.75 ; casein ratio ≥ 4.33). It is not easy to find the best cutoff point, because the choice should be based on the individual risk to an OFC which can vary under different circumstances. Therefore, we have to decide what is more important to consider in the result of the OFC, to make the cutoff point in its rightful place. For example, CM ratio 35.20 had 75% sensitivity and 59% specificity, namely, 41% of patients could be tolerant.

When comparing the four ROC curves that have statistical significance (specific IgE and ratios), no differences were found. Considering this, we cannot conclude that the ratio is a better predictive tool than specific IgE. However, in these children, casein ratio is a better predictive tool of tolerance than casein-specific IgE (Figs 1 and 2). Twenty-three children in the tolerant group ($n = 107$, 21.5%) showed CM-specific IgE > 2.5 KU/l (PPV 90%) and 7 (6.5%) with CM-specific IgE > 15 KU/l, nevertheless all of them tolerated. Accordingly, they accomplished our ratio criteria to undergo an OFC that if we had only used CM-specific IgE, it would not have been indicated.

In conclusion, CM and casein ratios tend to perform better than specific IgE in identifying tolerant patients in our series, but we cannot assess that CM and casein ratios are better tools than specific IgE to predict the tolerance according to prior studies.

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Soy allergy complicating disease management in a child with coeliac disease

To the Editor,

Food allergy is an immune-mediated reaction that occurs reproducibly on exposure to a certain food or food component (most commonly a protein) and is distinct from other conditions causing adverse responses to food, including digestive/absorptive processes, toxic reactions and autoimmune disorders (1). Coeliac disease (CD) is an autoimmune condition, which typically presents with gastrointestinal symptoms and failure to thrive within the first years of life and is caused by an abnormal immunological response to ingested gluten, in genetically predisposed individuals (2,3). Its diagnosis is primarily based on the presence of characteristic duodenal biopsy findings (villous atrophy, crypt hyperplasia and intra-epithelial lymphocytosis) along with documentation of clinical or histological response to a gluten-free diet (GFD) (4). The presence of positive serology for CD-specific autoantibodies, mainly endomysial and antitissue transglutaminase antibodies (EMA and tTG, respectively), is also a strongly supportive diagnostic finding, but not essential for diagnosis (2,4).

We herein report a rare and diagnostically challenging case of a 13 ½-year-old child with biopsy-proven CD and concurrent soy allergy complicating disease management, and briefly discuss the potential pitfalls associated with differential diagnosis and treatment of refractory symptoms in patients with CD.

A 13 ½-year-old girl was referred to the Allergy Department at 'Sotiria' General Hospital, Athens, Greece, for further evaluation of refractory CD. The patient had been diagnosed

with CD at the age of 3 ½ years, approximately 6 months following the onset of gastrointestinal symptoms (vomiting, abdominal pain, flatulence and diarrhoea) along with tiredness. Personal and family history for atopy was negative. Laboratory workup at the time of initial diagnosis was significant for positive EMA, tTG and antigliadin autoantibodies (AGA); duodenal biopsy was compatible with coeliac disease. Both mother and child tested negative for *Helicobacter pylori* antibodies. Repeat upper endoscopy with duodenal biopsies, performed twice at the age of 7 and 13 years, revealed similar findings to the initial biopsies (partial villous atrophy, increased number of intra-epithelial lymphocytes and moderate eosinophilic mucosal infiltration). During this period and despite a strict GFD, the patient's symptoms persisted, CD-specific autoantibodies remained positive, and declining growth percentiles were noted.

At the patients' presentation to our department, routine laboratory tests (including complete blood count with differential, electrolytes, blood glucose, renal and liver function tests, lipase, amylase, erythrocyte sedimentation rate, c-reactive protein) were within normal limits; quantitative Ig determination showed a moderate elevation of IgA in the serum (233 mg/dl, normal range: 85–214), while IgM and IgG values were normal. Serological testing for AGA (IgA and IgG) and t-TG IgA antibodies gave positive results (AGA IgA and IgG: 24 and 62 units, respectively, t-TG IgA: 83 units, normal values in all cases <20 units), while EMA antibodies were borderline positive (1:20). Molecular HLA typing confirmed the presence of the HLA-DQ2 and HLA-DQ8 haplotype. Skin prick