

ORIGINAL ARTICLE

A prediction rule for food challenge outcome in children

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To cite this article: Zomer-Kooijker K, Slieker MG, Kentie PA, van der Ent CK, Meijer Y. A prediction rule for food challenge outcome in children. *Pediatric Allergy Immunology* 2012; **00**.

Keywords

food allergy; food challenge; food challenge outcome; predictive model.

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Accepted for publication 17 December 2011

DOI:10.1111/j.1399-3038.2012.01266.x

Abstract

Background: In children with food-related symptoms, a food challenge is considered as the gold standard to diagnose allergy. If food allergy could be predicted by patient history and/or diagnostic tests, the number of time-consuming and sometimes risky food challenges could be decreased. We aimed to determine questionnaire and test-based characteristics, to predict the food challenge outcome (FCO) in children referred to a tertiary centre for the evaluation of food-related symptoms.

Methods: Pre-challenge standardized questionnaires, skin prick tests (SPT), and specific IgE levels (sIgE) were obtained in patients that underwent a food challenge in our hospital in 2009. Characteristics of patients with positive and negative FCO were compared, and uni- and multivariate associations between predictors and FCO were calculated. Based on the multivariate model, a risk score was developed to predict the FCO.

Results: One hundred and twenty-nine challenges were analyzed, 41.9% had a positive outcome. Median age of both groups was 4.9 yrs (range 2.8–8.3). Patients with a positive FCO reacted faster with symptoms after allergen ingestion and had higher sIgE levels compared to children with negative FCO. A clinical risk score was developed based on the index food, 'time between allergen ingestion and complaints' and sIgE levels (range 0–10). The prognostic capacity of this model (AUC) was excellent (0.90). The very high- and low-risk groups (24% of patients) are both predicted excellent without misclassification.

Conclusion: Positive FCO can be predicted by the index food, time between allergen ingestion and development of symptoms, and the sIgE level.

The term food allergy (FA) is used to describe an adverse effect on ingestion of a food caused by the immune system. Food allergy rates vary by age, local diet, and many other factors, but generally its prevalence is 2–6% (1, 2). The 2008 Centres for Disease Control and Prevention report indicated an 18% increase in childhood food allergy from 1997 to 2007.

The diagnosis of FA can be suspected on a combination of history and physical examination, while diagnostic tests, like skin prick test (SPT) and serum food-specific IgE (sIgE), can be helpful to differentiate between IgE-mediated and non-IgE-mediated complaints (3, 4). In clinical practice, a variety of adverse reactions that are not of allergic nature must be considered, and more than 20% of adults and children alter their diets for perceived food allergy (5, 6). To confirm the diagnosis of food allergy, the placebo controlled

food challenge is usually considered as the golden standard (7). However, this is time consuming, has cost expenses, has the risk of anaphylaxis, and requires a specialized setting and personnel.

An easy way to differentiate between children with a high and low suspicion of a food allergy would facilitate patient care and might reduce the number of food challenge tests in clinical practice.

Literature about the predictive value of diagnostic tests for food allergy is available (8–10). However, data on the combined predictive capacity of both patient characteristics and diagnostic tests are scarce, and very little literature is available on clinically useful risk models (11). In this study, we aimed to investigate the predictors of the outcome of food challenge tests (FCO).

Methods

Study population

The UMC Utrecht is a tertiary hospital providing specialized allergologic care. Children, aged 0–18 yrs, consulting an allergologist for a suspected food allergy receive a standardized questionnaire prior to their first visit to the outpatient department, which is filled in at home by the parents. All patients undergoing a challenge (medication or food) are registered in a database. Patients who underwent a food challenge and completed the questionnaire in 2009 were included in our study. Patients with inconclusive FCO's were excluded from analysis. Fig. 1 shows a flowchart of the selection of patients. All patients gave informed consent to the collection and analysis of their anonymized data gathered during regular hospital visits for medical purposes. Because this is an analysis of data gathered in routine clinical practice, formal approval of the ethics committee was waived.

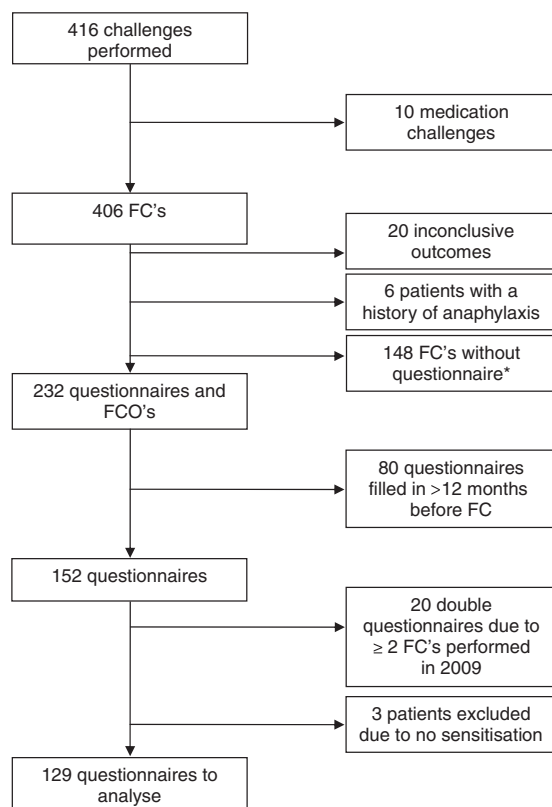
Measurements

From the questionnaire information regarding the history of allergic reactions, comorbidity, exposure to allergens and pollution, the family history, and general well-being of the patient was obtained. Based on the availability in our questionnaire and known risk factors from the literature, 21 can-

didate predictor variables were selected. Candidate predictor variables were patient characteristics (two variables), the potential allergen (one), family history (one), parental reported complaints independent of intake of potential allergen (five), factors associated with intake of potential allergen (nine), exposure to pets (one), and outcome of diagnostic tests (two) (Table 1).

Sensitization was established by measuring specific immunoglobulin E level (sIgE) or by performing a SPT against the suspected allergen. sIgE was measured in serum, using the CAP system FEIA (Pharmacia Diagnostic, Uppsala, Sweden). A positive test result was defined as a sIgE level above 0.35 kU/l (10, 12). Skin prick test was performed according to the EAACI guidelines (13), using commercially available extracts (ALK, Abelló, Nieuwegein, The Netherlands), or fresh material (in case of a fruit allergy) and compared with a negative – (glycero-saline) and a positive control (histamine HCL). Antihistamine medication was withheld for at least 72 h prior. The test was performed on the back of the child, and the resulting wheal was measured after 15 min. A positive SPT was defined as a wheal ≥ 3 mm larger than the negative control (9).

All peanut, hazelnut and cow's milk challenges were performed as double-blind placebo controlled food challenge (DBPCFC) according to the EAACI guidelines and the local protocol (14, 15).



* These patients are seen by general paediatricians or subspecialists other than allergologists and therefore not sent a questionnaire before their outpatient department visit.

Fig 1 Selection of patients and questionnaires for analysis.

*These patients are seen by general pediatricians or subspecialists other than allergologists and therefore not sent a questionnaire before their outpatient department visit.

Table 1 Characteristics of the population, and univariate relationship with a positive FCO

	All children (n = 129) n (%)	Positive FCO (n = 54) n (%)	OR for positive FCO	p-value
Patient characteristics				
Male sex	81 (63)	32 (60)	0.81	0.572
Age at time of the FC (yrs)	4.9 (2.9–8.3)*	4.9 (3.0–7.3)*	0.956	0.325
Challenged food				
Peanut (DBPCFC)	30 (23)†	12 (22)	3.56	0.083‡
Hazelnut (DBPCFC)	16 (12)†	5 (9)	2.42	0.285
Cow's milk (DBPCFC)	27 (21)†	12 (22)	4.27	0.050 ‡
Egg (OFC)	26 (20)	16 (29)	8.53	0.004 ‡
Nuts (OFC)	9 (7)	7 (13)	18.67	0.004 ‡
Other (OFC)	21 (16)	3 (6)	–	Reference
Family history				
Positive for atopic diseases	100 (78)	43 (80)	1.02	0.969
Parental reported complaints of child, independent of ingestion of potential allergen				
Eczema	108 (84)	47 (86)	1.13	0.800
Allergic rhino conjunctivitis	45 (35)	20 (37)	1.07	0.866
Asthma	52 (40)	27 (50)	1.36	0.405
Urticaria	44 (34)	22 (41)	1.66	0.181
Allergic complaints provoked by pets	63 (49)	34 (63)	2.31	0.025 ‡
Parental observed complaints provoked by specific food intake				
Mouth: swelling lips/tongue, itchiness	59 (46)	31 (57)	2.18	0.143
Nose: sneezing, rhinorrhea	27 (21)	11 (20)	0.87	0.835
Eye: tears, itchiness	42 (33)	17 (27)	0.85	0.739
Skin: redness, urticaria, increase of eczema	93 (72)	39 (72)	0.94	0.917
GIT: stomachache, diarrhea, vomiting	58 (45)	23 (42)	0.79	0.604
Pulmonary: coughing, dyspnoea	38 (29)	15 (28)	0.88	0.775
Cardiovascular: hypotension, fainting	6 (5)	18 (33)	0.59	0.525
Time within reaction is provoked by ingestion				
<5 min	67 (52)	32 (59)	7.34	0.044 ‡
5–60 min	49 (38)	21 (39)	6.29	0.089‡
>60 min	14 (11)	2 (4)	–	Reference
Smallest amount provoking a reaction				
Tip of knife	81 (63)	37 (69)	0.00	0.754
More than a tip of knife	47 (36)	17 (31)	0.00	0.867
Pets ownership				
Cat	27 (21)	7 (13)	0.40	0.059
Dog	19 (15)	6 (11)	0.59	0.327
Horse	9 (7)	3 (6)	0.69	0.623
Rabbit	13 (10)	4 (7)	0.59	0.413
Diagnostic test results				
Positive SPT	88 (68)	43 (80)	2.49	0.064‡
Specific IgE level				
<0.35	26 (20)	2 (4)	–	Reference
0.35–0.7	10 (8)	1 (2)	1.28	0.848
0.7–3.5	34 (26)	16 (30)	10.24	0.004 ‡
3.5–17.5	30 (23)	14 (26)	10.42	0.005 ‡
17.5–50	16 (12)	10 (19)	17.13	0.002 ‡
50–100	13 (10)	12 (22)	141.64	0.000 ‡

DBPCFC, double-blind placebo controlled food challenge; FC, food challenge; FCO, food challenge outcome; OR, odds ratio; SPT, skin prick test.

Bold data are significantly related to the outcome, $p < 0.05$.

*Data are presented as median $\pm$ interquartile range.

‡Included in the multivariate logistic regression model.

Challenges with other foods were performed as open challenges. Indications to perform a food challenge are sensitization to the allergen confirmed by a SPT or sIgE, positive history of an allergic reaction to a specific allergen, or currently avoiding eating this potential allergen. A FCO was considered positive and terminated when at least one of the following reaction occurred: (i) objective symptoms indicative of an allergic reaction (as urticaria, facial swelling, rhinoconjunctivitis, vomiting, diarrhea, dyspnea, bronchoconstriction, and hypotension), or (ii) subjective complaints (abdominal pain, nausea) after at least three subsequent doses. The most severe symptoms were scored based on the Sampson-score by the specialist to measure severity (16). A FCO was considered inconclusive when the criteria for a positive FCO could not be met, or when the test material was refused.

Subsequently, patients were observed for 2 h in case of a negative outcome, and 4 h in case of a positive outcome. One day after the challenge, a phone call was made

Table 2 Independent predictors of a positive food challenge outcome

Predictor variable	OR*	Beta	Points
Allergic reaction			
Acute (within 5 min)	3.08	1.126	1
Subacute (5–60 min)	1.88	0.632	0.5
Late (>60 min)	Reference	-	-
Specific IgE level (kU/l)			
<0.35	Reference	-	-
0.35–0.7	3.27	1.186	1
0.7–3.5	16.04	2.775	2.5
3.5–17.5	32.84	3.491	3
17.5–50	125.90	4.835	4.5
50–100	2146.09	7.671	7
Tested food			
Peanut	7.27	1.985	2
Hazelnut	0.87	-0.135	0
Cow's milk	20.1	3.001	2.5
Egg	33.6	3.515	3
Nuts	291.6	5.676	5
Other	Reference	-	-
ROC area	0.904		0.900
	(0.85–0.96)		(0.85–0.95)
Hosmer-Lemeshow**	5.88		
	(p = 0.634)		

ROC, receiver operator characteristics; OR, odds ratio; SFA, suspected food allergen.

*Adjusted for overoptimism by bootstrapping.

**Chi-square and significance.

Individual score = $0.5 \times$ Subacute complaints (yes = 1, no = 0) + $1 \times$ Acute complaints (yes = 1, no = 0) + $1 \times$ sIgE level between 0.35 and 0.7 (yes = 1, no = 0) + $2.5 \times$ sIgE level between 0.7 and 3.5 (yes = 1, no = 0) + $3 \times$ sIgE level between 3.5 and 17 (yes = 1, no = 0) + $4.5 \times$ sIgE level between 17.5 and 50 (yes = 1, no = 0) + $7 \times$ sIgE level between 50 and 100 (yes = 1, no = 0) + $2 \times$ SFA peanut (yes = 1, no = 0) + $2.5 \times$ SFA cow's milk (yes = 1, no = 0) + $3 \times$ SFA egg (yes = 1, no = 0) + $5 \times$ SFA nuts (yes = 1, no = 0).

to evaluate whether late symptoms developed. A positive FCO was considered as the gold standard for the diagnosis of food allergy in this study. Patients with a previous anaphylaxis, that were challenged to test the severity of the current reaction, were not included in this analysis (n = 6).

Statistical analysis

The predictors 'amount of ingested allergen provoking complaints', 'time lag between ingestion and development of symptoms', the challenge food, and the sIgE level were defined as a categorical variable. All remaining variables were dichotomized.

Univariate associations between candidate predictor variables and the outcome of a positive food challenge were investigated by univariate logistic regression. In the eligible study population, the overall proportion of missing data on candidate predictor variables was 9.6%. In a standard complete case analysis, subjects with one or more missing values are excluded from analysis. To avoid bias that might result from a complete case analysis, our missing data were imputed by using multiple imputations (17). Predictors that were univariately associated with the outcome (with a p-value < 0.15), and unrelated to clinical treatment, were included in stepwise backward fashion selection in a multivariate logistic regression model to evaluate their independent value (p-value < 0.05) in the prediction of a positive outcome of a food challenge. Reliability (of goodness of fit) was estimated using the Hosmer-Lemeshow test.

Subsequently, the prognostic capacity to differentiate between a patient with and without a positive FCO was estimated using the area under the receiver operating characteristics curve (AUC). An AUC of 0.9 and above is considered excellent for a prognostic model (18). Internal validation of the final model was performed by using the bootstrap resampling technique. The calculated regression coefficients were

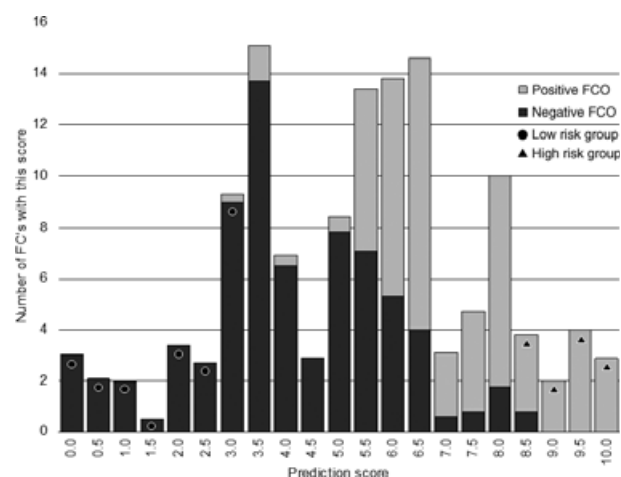


Fig 2 The distribution of positive and negative FCO's by prediction score (imputed data).

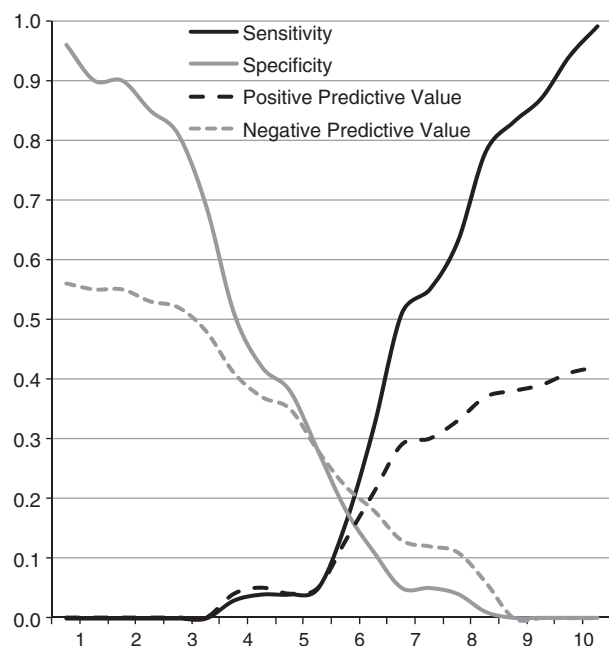


Fig 3 Test characteristics at various cutoff points.

equally modified to create a simple risk score for use in clinical practice. Multivariate regression analyses, imputation, and model validation were performed with the statistical program PASW Statistics 18 (version 18.0.0; SPSS Inc., 2009, Chicago, IL, USA).

Results

In 2009 a total of 129 children underwent food challenge and had a valuable questionnaire. Missing data (9.6%) in the questionnaires were imputed. Median age was 4.9 yrs, and food challenges were more often performed in boys (83 vs. 49 girls, NS). Of all 129 food challenges, 57 challenges (41.9%) had a positive outcome (Table 1). Most frequently performed food challenges were peanut (23.5%), cow's milk (25.0%), egg (19.7%), and hazelnut (12.9%). Table 1 shows the characteristics of all patients and the characteristics of patients with a positive FCO.

Univariate analysis

Two questionnaire variables were positively associated with a positive FCO: symptoms developing within 5 min after ingestion of the allergen ($p = 0.033$), and complaints provoked by pets ($p = 0.05$). The other questionnaire variables were not significantly associated with the FCO. The index foods cow's milk ($p = 0.05$), egg and nuts (both $p = 0.004$) were also strongly associated with a positive FCO. Sensitization to an allergen as presented as a level of specific sIgE > 0.7 was strongly associated with a positive FCO (p -values for different categories, see Table 1). Based on the p -values and the incidence of positive FCO's in our population, five variables were included in the multivariate analysis (Table 1).

Predictive model

After stepwise multivariate analysis of the selected variables, independent predictors were: (i) the index food, (ii) sIgE level, and (iii) time lag between food ingestion and development of allergic response. To develop a predictive model, the regression coefficients were calculated, and points were assigned to each of those three variables. Subsequently, for every child, a score, ranging from 0 to 10, was calculated based on the equation shown below Table 2. The discriminative power of this model was 0.90, which is excellent for a prognostic model, defined as a AUC of 0.9 and above. The scores and corresponding numbers of patients with their FCO are shown in Fig. 2.

The prediction scores and the corresponding numbers of positive and negative food challenge (FC) outcomes are shown in Fig. 2. Fig. 3 shows the test characteristics at different cutoff values.

The very high- and low-risk groups, with scores ≥ 9 and ≤ 3 , respectively ($n = 9$ and $n = 23$, respectively, see Fig. 2), are both predicted excellent without any misclassification. Therefore, extrapolating from the current sample, the total number of food challenges could be decreased with 24% when those two patient categories would not be challenged. If the scores between 3.5 and 5 ($n = 33$) would be added to the low-risk group to predict the FCO, 97% (63 out of 65) of the patients within the high- and adjusted low-risk groups would be predicted adequately. The total number of challenges could then be decreased with 50%, when accepting this misclassification of 3%. Prediction for the intermediate group remains difficult.

Discussion

In this study, we show that in a group of hospital patients, a short time lag between food ingestion and allergic response together with a positive sIgE level and the index food can acceptably predict a positive FCO. However, in individual patients, a sure prediction can be reached in 24.0%.

Our findings that increasingly higher concentration of food-specific IgE antibodies is correlated with an increasing risk for a clinical reaction are consistent with literature (6, 19). There are a number of reports about predictive values of diagnostic tests for the outcome of food challenges in children (20–22). Food-specific IgE antibody levels, with cutoff values with a positive predictive value (PPV) $> 95\%$, have been defined for different foods (7, 23). However, those values may not be applicable in all settings because of methodological differences in challenge protocols between hospitals and differences in patient populations (age, nuances in diets) (24). We have also studied questionnaire-based factors and combined the independent risk factors with the outcome of the FC, resulting in a simple prediction rule for daily clinical use.

There are some limitations that should be considered when interpreting the results. Firstly, the diagnosis food allergy was made based on the questionnaire, sensitization, and a

food challenge. In our setting, not all challenges are performed in a double-blind, placebo controlled (DBPC) manner. In the high-risk group, 2 out of 9 FC's were not performed in a double-blind manner. Open challenges may have false positive results, as shown in cow's milk allergy studies ranging from 50 to 68% depending on the setting where the OFC's are performed (4, 25). This may have overestimated the total correct predicted percentage of patients to some degree. However, this effect might be neutralized in our study, because the size of the low-risk patient group may possibly have been larger if all FC's would have been performed in a DBPC manner. Secondly, the retrospective design of our study has resulted in a number of missing values, which can lead to considerable loss of power in a multivariate analysis. We therefore imputed missing values, which we believe lead to unbiased complete results (26). Thirdly, in this study, we did a proper internal validation of the model. However, as in every study with regard to prediction models, the model asks for additional external validation and, of course, the use of the model should be limited to the tertiary clinical setting.

Our model consists of three factors, namely the index food, the time gap between ingestion and the development of symptoms, and the level of sIgE. Scarce literature is available about the exact time within symptoms develop after ingestion of food in patients with a IgE-mediated food allergy. Generally, it is assumed that allergic reactions mediated by specific IgE antibodies are typically developed rapidly, usually within minutes (27). However, they may also be delayed by up to an hour and rarely by up to a few hours (28). Our study shows that rapid onset symptoms, developing within 5 min after ingestion, are associated with a higher risk on a positive FC outcome. This may be partially explained by the high prevalence (72.5%) of IgE-mediated cutaneous reactions in our population, but also other organ systems may respond with IgE-mediated allergic symptoms within minutes. Late complaints are more likely to be caused by another cause than food allergy (28).

In our population, a positive SPT was not an independent predictor for a positive FCO and was therefore not included in the prediction model. There is literature that shows that in skin testing, wheal diameters >7 or 8 mm are highly predictive of clinical allergy to peanut, cow's milk, or egg allergy (29, 30). In our study, the SPT result was dichotomized in positive or negative. This might have negatively influenced the predictive capacity of the SPT in our population. However, a recent study shows that also a dichotomized SPT results does significantly contribute to the accuracy in predicting a FCO (11).

Age, which was an independent predictor in that same study, was not an independent predictor in our model. This

may be explained by the age difference between the two cohorts (mean age difference 1–3 yrs). We have described several variables that were significantly related to a positive food challenge outcome. Those variables depend on the availability in our dataset, which was based on a questionnaire and diagnostic test results. This might have resulted in a difference in variables in our model, compared to previous literature. Also the accuracy of filling in a (not previously validated) questionnaire might have led to differences, as the history of symptoms, which were not related to the FCO in our cohort. Many children in our study had multiple sensitizations to food allergens and had complaints to more than one food. Those symptoms, for different foods, were marked in one table. Symptoms were classified according to the Sampson criteria. However, filling in this large table might still have led to more inaccuracy then specifically asking parent or child for the symptoms provoked by ingestion of an allergen.

A 100% correct prediction of a FCO was possible in 24.0%. We do realize that in clinical setting, food challenges are also used to reject a diagnosis. Therefore, if non-specific symptoms do develop in the low-risk group after reintroduction at home, preferably a DBPCFC can be performed to prevent unnecessary restriction of the diet. In high-risk patients, it is advisable to periodically check the level of sIgE, to assess whether the risk of the patient to respond positive to a FC has decreased (based on the risk score and literature (6)). If this is the case, a FC may be useful to assess whether restriction of the diet is still necessary. If in clinical practice the prediction rule would be used with less strict criteria, cut-off values of ≤ 5 and ≥ 9 can be used. In patients with low scores, the FC might be postponed or skipped, because the risk on an unexpected (positive) outcome is only 3.6%.

Whether our prediction rule is a useful rule in clinical decision-making, internal and external validation has to show. Future research should be aimed to determine prediction rules that are useful in primary and secondary healthcare institutions.

Food challenges do often have negative outcomes, in our population in 58.2%. A positive FCO outcome can be well predicted by using a rule, consisting of a risk score based on three variables: the index food, the time gap between ingestion and the development of symptoms, and the sIgE level, with a AUC of 0.90. Using this rule as a clinical guideline may decrease the number of food challenges with 24% with a 100% certainty in a tertiary-centre setting or, when accepting a proportion of 3.3% wrongly classified, with 46%. However, in the majority of patients (54%), a food challenge remains the golden standard to confirm or reject the diagnosis of food allergy.

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