Challenges in egg allergy: a retrospective look at the utility of cut-off values

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To the Editor,

Egg allergy is a prevalent and clinically significant condition in pediatric populations, demanding precise diagnostic procedures like oral food challenges (OFCs) (1,2). Recently, the European Academy of Allergy and Clinical Immunology (EAACI) has formulated distinct IgE cut-off values to refine patient selection regarding OFCs with both baked (BE) and cooked egg (CE) forms (3).

Considering the newly developed EAACI guideline cut-offs, as well as the systematic review presented at FAAM 2022, a retrospective analysis was conducted to evaluate the results of pediatric OFCs performed from 2015 to 2022 within our Allergy Department. Specific IgE cut-off values for ovomucoid (OVM) (0.8kU/L) and egg white protein (EWP) (3.8 kU/L for CE and 8.0 kU/L for BE) were compared to the OFCs outcomes. Demographics, clinical data and IgE levels to different egg proteins were also collected.

A total of 70 children were included, predominantly males (57.1%), with a median age of the index reaction at 1.67 years (IQR 1-3). Concerning the spectrum of egg forms, the majority of reported reactions occurred with CE (n=55;78.6%).

The most frequently reported manifestations were mucocutaneous symptoms (74.3%), mostly exanthema, urticaria and angioedema, with 22.9% experiencing eczema exacerbation after food intake. Gastrointestinal symptoms were observed in 38.6% of cases, whereas respiratory manifestations were reported in 11.4%. Fifteen children (21.4%) presented with anaphylaxis.

Among our cohort, 75.7% had rhinitis/rhinoconjunctivitis; 64.3% atopic dermatitis and 52.3% asthma/recurrent wheezing. Additionally, 31.4% had a history of coexisting confirmed or suspected cow's milk allergy. Demographic and clinical data are represented in **table I**.

Overall, 87 OFCs were conducted (1.2/children), of which 56.3% were with CE and 43.7% with BE, with a total of 12 (13.8%) positive OFCs. Among positive OFC cases, mucocutaneous symptoms were prevalent (n=9, 75.0%), with gastrointestinal symptoms reported in 3 cases (25.0%), and respiratory symptoms in 2 (16.7%). Only one child (8.3%) reacted after reaching cumulative dosage (~20g) in the OFC protocol, with 91.7% reacting mid-OFC.

Symptoms in 10 out of the 12 positive OFC cases (83.3%) aligned with the index-reaction, though none progressed to an anaphylactic reaction.

Regarding CE OFCs, 12.2% of children had a positive OFC; 83.3% of children with positive OFCs exhibited sIgE levels to egg white below the cut-off, while 33.3% had OVM sIgE below the threshold. Conversely, 14.0% of negative OFCs exceeded the EWP sIgE cut-off, and 30.2% exceeded the OVM cut-off. In OFC with both sIgE levels below the cut-offs, 33.3% were positive and 65.1% were negative.

In the BE OFCs there were 15.8% of positive challenges, 50.0% of which had EWP sIgE levels above 3.8 kU/L, while only 3.1% of negative OFC exceeded this cut-off. Results are shown in **table II**.

Among all CE OFCs, elevated OVM sIgE and total IgE levels were indicative of a positive OFC. Notably, these associations remained statistically significant in the sub-group of the 42 CE OFCs with EWP sIgE below the cut-off. No correlation was found between OFCs outcomes, in both BE and CE forms, regarding gender, median age of allergy onset, clinical presentation or personal history of atopy.

Predictors of OFC outcomes play a pivotal role in refining diagnostic accuracy in pediatric allergy (3,4). This analysis underscores the importance of a comprehensive approach to egg OFC, highlighting the value of complementary testing, including diverse egg protein-specific IgE measurements in enhancing decision-making (5,6).

The use of a single EAACI cut-off to predict OFC results lead to large proportions of patients yielding contradicting results. Conversely, the integration of dual IgE cut-offs in CE OFCs showed significant value.

Notably, higher OVM sIgE levels associated with positive OFC with CE among children with EWP IgE levels below the cut-off, further reinforcing the value of this complementary approach.

Additionally, integrating skin tests (which also have EAACI cut-offs) in future studies could further enhance the accuracy of predicting egg OFC outcomes (3,7).

Nevertheless, the varying cut-off values among populations underscore the necessity for customized thresholds, taking into account comorbidities, IgE trends, and national considerations, while never undermining the role of OFCs as the definitive diagnostic test in determining food allergy status.

Systematic longitudinal analysis of the application of the EAACI cut-offs would be instrumental for refining diagnostic approaches and advancing the management of this prevalent pediatric condition.

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Contributions

PBA Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Writing – original draft
HPP Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Writing – original draft
MIPC Conceptualization, Formal Analysis, Resources, Supervision
GL Formal Analysis, Resources, Supervision
IFCF Data Curation, Investigation
ML Data Curation, Investigation
TMF Data Curation, Investigation
AMPTFC Resources, Supervision

Conflicts of Interests

None.

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Table I: Demographic and clinical data

Variables	Total (n=70) (n;%)
Male gender	40 (57.1)
Age (years), median	1.67 (IQR 1-3)
Patients with onset reaction to cooked egg	55 (78.6)
Reported symptoms	
Mucocutaneous	52 (74.3)
Exanthema/urticaria/angioedema	36 (51.4)
Eczema exacerbation	16 (22.9)
Gastrointestinal	27 (38.6)
Respiratory	8 (11.4)
Anaphylaxis	15 (21.4)
Rhinitis/rhinoconjunctivitis	53 (75.7)
Atopic dermatitis	45 (64.3)
Asthma/ recurrent wheezing	37 (52.3)
Concomitant Cow milk allergy	22 (31.4)

Table II: Results of egg oral food challenges

Categorical Variables (n; %) / Numerical variables (median - IQR)	**Egg OFCs** (n=87)							
	Cooked (n=49; 56.3)				**Baked** (n=38; 43.7)			
	Total (n=49;100)	**Positive** (n=6;12.2)	**Negative** (n=43;87.8)	*p-value*	**Total** (n=38; 100)	**Positive** (n=6;15.8)	**Negative** (n=32;84.2)	*p-value*
Age at Egg OFC (years)	6.67 (4-10)	10.5 (4.17-11.53)	6.33 (4-9.33)	0.547	7.63 (5-9)	5.08 (4.25-7.00)	8.16 (5.92-11.5)	0.060
Age of IgE measurement (years)	5.5 (3-10)	10 (4-11)	5 (3-9)	0.182	7 (4-9)	4.5 (3-7)	7.62 (0.069)	0.069
Time from IgE measurement to OFC (years)	0.5 (0.2-0.8)	0.25 (0.17-0.5)	0.5 (0.25-0.92)	0.182	0.75 (0.2-1)	0.25 (0.17-1.17)	0.92 (0.12-1.00)	0.669
Time from index reaction to OFC (years)	4.25 (0.92-8)	7.50 (3-8.33)	4.25 (0.67-7)	0.349	4.12 (3-7.33)	3.46 (1.33-4)	5.12 (3.12-8.08)	0.095
IgE to egg white (EWP) (k/UI)	0.91 (0.32-2.37)	1.95 (0.65-2.57)	0.83 (0.32-2.28)	0.248	1.26 (0.57-5.56)	4.82 (0.51-12.1)	1.23 (0.57-4.70)	0.385
IgE to ovomucoid (OVM) (k/UI)	0.30 (0.04-1.26)	1.88 (0.76-3.46)	0.19 (0.04-1.09)	**0.005**	0.82 (0.24-1.85)	4.46 (0.45-11.7)	0.74 (0.18-1.68)	0.074
Total IgE (k/UI)	141 (37-885)	1070 (508-1770)	134 (29-565)	**0.041**	413 (106-1675)	340 (72-556)	418 (108-1834)	0.464
Children with IgE to EWP *above* the cut-off * n (%)	7 (14.3)	1 (16.7)	6 (14.0)		4 (10.5)	3 (50.0)	1 (3.1)	
Children with IgE to EWP *below* the cut-off * n (%)	42 (85.7)	5 (83.3)	37 (86.0)		34 (89.5)	3 (50.0)	31 (96.7)	
Children with IgE to OVM *above* the cut-off (0.8 kU/L) n (%)	17 (34.7)	4 (66.7)	13 (30.2)					
Children with IgE to OVM *below* the cut-off (0.8 kU/L) n (%)	32 (65.3)	2 (33.3)	30 (69.8)					
Children with IgE to EWP and OVM both IgEs *above* the cut-off n (%)	6 (34.7)	2 (33.3)	4 (9.3)					

Children with IgE to EWP and OVM both *below* the cut-off n (%)	30 (34.7)	2 (33.3)	28 (65.1)	

*****- Egg white cut-offs: **cooked** – 3.8 kU/L; **baked** – 8.0 kU/L; statistically significant in **bold** ($p<0.050$);
EWP: egg white protein; IQR - interquartile range.OFCs: oral food challenges; OVM: ovomucoid