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Specific IgE Decision Point Cutoffs in Children with IgE-Mediated Wheat Allergy and a Review of the Literature

François Graham[a, b] Jean Christoph Caubet[a] Salim Ramadan[a] David Spoerl[c, d] Philippe A. Eigenmann[a]

[a]Pediatric Allergy Unit, University Hospitals of Geneva and University of Geneva, Geneva, Switzerland; [b]Department of Allergy and Immunology, Centre Hospitalier Universitaire Sainte-Justine and Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [c]Division of Clinical Immunology and Allergy, Department of Medical Specialties, University Hospital and School of Medicine, Geneva, Switzerland; [d]Division of Laboratory Medicine, Department of Pathology, Genetics and Laboratory Medicine, Geneva University Hospitals, Geneva, Switzerland

Keywords
Wheat allergy · Children · Food allergy · Component testing · Omega-5 gliadin · Wheat-specific IgE · Oral food challenge

Abstract
Background: Wheat IgE-mediated food allergy in children is one of the most frequent food allergies in westernized countries, affecting between 0.4 and 1% of children. Although 95% predictive decision points have been determined for major allergens such as peanut, egg, and milk, the diagnostic performances of wheat-specific IgE (sIgE) and wheat component testing are not well established. ***Objectives:*** The aim of this study was to determine sIgE decision point cutoffs in children with IgE-mediated wheat allergy and provide a review of the literature. ***Method:*** A retrospective review of wheat oral food challenges was performed at the pediatric allergy unit of the University Hospitals of Geneva between 2004 and 2019. Performance characteristics for wheat and ω-5 gliadin sIgE were calculated and positive and negative OFC data were compared using the Mann-Whitney U test. ***Results:*** A wheat sIgE cutoff of 2.88 kU_A/L had a sensitivity of 95% (negative decision point), whereas a cutoff of 78.1 kU_A/L had a specificity of 95% (positive decision point). When giving equal weight to sensitivity and specificity, the optimal cutoff point for wheat sIgE was 12 kU_A/L, which gave a specificity of 70% and a sensitivity of 66.67%. ***Conclusions:*** These findings suggest a high positive decision point for wheat sIgE (78.1 kU_A/L). This reinforces the importance of considering OFC in children with IgE-mediated wheat allergy to confirm diagnosis even in patients with relatively high wheat sIgE values, as there is a risk of falsely mislabeling these patients as allergic.
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Introduction

Wheat IgE-mediated food allergy in children is one of the most frequent food allergies in westernized countries, affecting between 0.4 and 1% of children [1]. Wheat products are ubiquitous and difficult to avoid, which can

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www.karger.com/iaa

Dr. François Graham
Pediatric Allergy Unit, University Hospitals of Geneva
6 rue Willy-Donze
CH–1211 Geneva 14 (Switzerland)
francois.graham@umontreal.ca

Table 1. Patient challenge characteristics

	Total	Positive OFC	Negative OFC	*p* value[b]
Challenges	50 (100)	30 (60)	20 (40)	
Male	36 (72)	24 (80)	12 (60)	0.21
Age at OFC date, years	4.04 (0.76–12.3)	4.65 (0.76–11.3)	2.98 (1.14–12.3)	0.20
sIgE, kU_A/L[a]				
Wheat (*n* = 50/50)	13.2 (0.27–100)	89.95 (1.2–100)	6.345 (0.27–78.4)	**<0.001**
ω-5 gliadin (*n* = 23/50)	0.56 (0–42.3)	0.935 (0–42.3)	0 (0-4.08)	0.057

Data are presented as the median (range) or *n* (%). OFC, oral food challenge.
[a] The median delay between sIgE and OFC was 4 months (range 0–13).
[b] Comparison between positive and negative wheat OFC.

greatly impact the quality of life of children and their families. Although 95% predictive decision points have been determined for major allergens such as peanut, egg, and milk [2, 3], the diagnostic performances of wheat-specific IgE (sIgE) and wheat component testing are not well established.

Materials and Methods

We performed a retrospective review of wheat oral food challenges (OFCs) performed at the pediatric allergy unit of the University Hospitals of Geneva between 2004 and 2019. Children with a history of immediate IgE-mediated reactions and wheat sensitization with primary wheat avoidance were included. Patients with wheat-dependent exercise-induced anaphylaxis, and non-IgE-mediated wheat allergy were excluded. OFCs were performed and interpreted according to PRACTALL guidelines [4] and severity of reactions graded using the Sampson severity scale [5]. All wheat and ω-5 gliadin sIgE were performed with the UniCAP™ system (Thermo Fisher, Uppsala, Sweden). Performance characteristics for wheat and ω-5 gliadin sIgE were calculated, and positive and negative OFC data were compared using the Mann-Whitney U test. Statistical analyses were performed using MedCalc (MedCalc Software, Ostend, Belgium) and GraphPad Prism version 8.0.1 (GraphPad Software Inc., San Diego, CA, USA). The project was approved by Geneva's Cantonal Research Ethics Committee.

Results

Forty-two children aged 1–12 years (median age 4 years) underwent 50 wheat OFCs. The patient challenge characteristics are described in Table 1. Thirty OFCs (60%) were positive and 20 (40%) were negative. Skin symptoms were most frequently encountered and developed in 24/30 patients (80%). Respiratory symptoms occurred in 15/30 (50%), whereas head, eyes, ears, nose, and throat – HEENT – symptoms occurred in 9/30 (30%) and gastrointestinal symptoms in 8/30 (26.7%). The median severity grade [5] was 3.5 (range 1–4). Overall, 21/30 (70%) were treated with an anti-histamine, 5/30 (16.7%) with corticosteroids, and 5/30 (16.7%) with epinephrine. All symptoms occurred within the dose escalation period or 2-h surveillance period at the end of OFC, except for 1 patient who passed the OFC but had an immediate reaction the following day when introducing wheat (spaghetti) at home. This patient was considered as a positive OFC.

Median wheat sIgE levels in the positive OFC group were significantly higher than in the negative OFC group (89.95 kU_A/L, range 1.2–100, and 6.345 kU_A/L, range 0.27–78.4, respectively, $p < .001$). The median ω-5 gliadin level was 0.935 kU_A/L (range 0–42.3) in the positive OFC group (16/23), with a trend towards higher values than in the negative OFC group (median of 0 kU_A/L, range 0–4.08, 7/23), while not reaching statistical significance ($p = 0.057$). The median sIgE to wheat was significantly higher in patients aged 5 years and older ($n = 20$, 49.15 kU_A/L, range 1.95–100) compared to patients 4 years and younger ($n = 30$, 9.445 kU_A/L, range 0.27–100, $p = 0.048$). No significant difference in median ω-5 gliadin sIgE levels was seen between these two age groups (0.295 kU_A/L, range 0–24.7, and 0.62 kU_A/L, range 0–42.3, respectively, $p = 0.93$). There was a trend towards more severe reactions in patients with higher wheat sIgE, although this was not statistically significant (grade 3 and 4 reactions compared to grade 1 and 2 reactions; median 100 kU_A/L, range 7.37–100, vs. 41.2 kU_A/L, range 1.2–100, respectively, $p = 0.095$). On the other hand, ω-5 gliadin sIgE levels did not correlate with reaction severity (grade 3 and 4 reactions compared to grade 1 and 2 reactions; median 0.62 kU_A/L, range 0–42.3, vs. 2.14 kU_A/L, range 0–24.4, respectively, $p = 0.61$).

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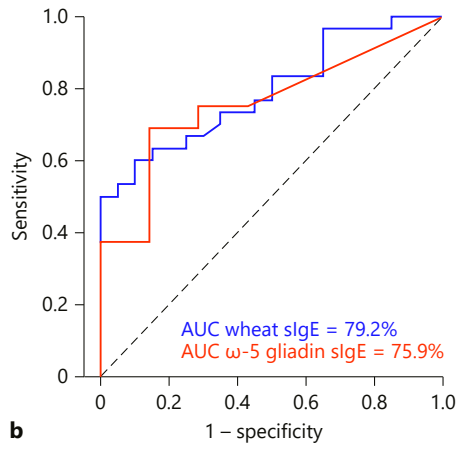
Wheat sIgE, kU_A/L	Sensitivity	Specificity
2.88[a]	95%	35%
12[b]	66.67%	70%
78.1[c]	50%	95%
ω-5 gliadin sIgE, kU_A/L	**Sensitivity**	**Specificity**
0[a]	95%	57.14%
0.06[b]	68.75%	71.43%
3.4[c]	37.5%	95%

a



b

Color version available online

Fig. 1. a Sensitivity and specificity for various wheat (n = 50) and ω-5 gliadin (n = 23) sIgE cutoffs. **b** ROC curve comparing the performance of wheat sIgE and ω-5 gliadin. [a] The negative decision point is defined as the cutoff producing a sensitivity of 95%. [b] The optimal cutoff point is the point where equal weight is given to sensitivity and specificity. [c] The positive decision point is the cutoff producing a specificity of 95%.

The performance characteristics of sIgE are reported in Figure 1a. A wheat sIgE cutoff of 2.88 kU_A/L had a sensitivity of 95% (negative decision point), whereas a cutoff of 78.1 kU_A/L had a specificity of 95% (positive decision points). When giving equal weight to sensitivity and specificity, the optimal wheat sIgE cutoff point was 12 kU_A/L, which gave a specificity of 70% and a sensitivity of 66.67%. A ω-5 gliadin sIgE cutoff of 0 kU_A/L had a sensitivity of 95%, whereas a ω-5 gliadin sIgE cutoff of 3.4 kU_A/L had a specificity of 95%. The optimal cutoff point for ω-5 gliadin was 0.06 kU_A/L, which gave a sensitivity of 68.75% and a specificity of 71.43%. AUCs for sIgE to wheat and ω-5 gliadin were not statistically different (79.2 vs. 75.9%, $p = 0.78$; Fig. 1b). Wheat sIgE performance characteristics were not influenced by age (AUC 78.0% for children 5 years and above compared to an AUC of 77.3% for children 4 years and below, $p = 0.96$).

Discussion

Our data on wheat sIgE are consistent with previous cutoffs described in the literature in children from Japan, Scandinavia, and the USA (Table 2). Overall, these data support a high positive decision point varying from 26 to 74.5 kU_A/L [2, 6, 7], with a negative decision point around 1 kU_A/L, and an optimal cutoff point from 10.1 to 15.7 kU_A/L. In our study, 18/20 patients with sIgE under the positive cutoff point (78.1 kU_A/L) would have been inadequately classified as wheat allergic on the basis of positive sIgE (>0.35 kU_A/L), if OFC had not been performed. This emphasizes the importance of performing OFCs to confirm wheat allergy, even in patients with positive wheat sIgE. The choice of the cutoff used can be adapted depending on the physician's clinical evaluation and the risk the physician is willing to accept taking into account the setting in which OFCs are performed. For example, the negative decision point (2.88 kU_A/L) could be used in a high-risk setting such as outpatient practice, whereas more at risk challenges using a cutoff under the positive decision point (78.1 kU_A/L) could be performed in a hospital setting, taking into account the physician's clinical evaluation.

ω-5 gliadin sIgE was only performed in a subgroup of patients (n = 23). Although both wheat and ω-5 gliadin yielded similar diagnostic performances (Fig. 1b), classification of a few patients differed when using these two tests with a cutoff of 0.35 kU_A/L: 5 patients with positive OFCs and positive wheat sIgE would have been falsely classified as negative on the basis of ω-5 gliadin sIgE values (lower sensitivity). On the other hand, 6 patients with a negative wheat OFC would have been correctly classified as negative with ω-5 gliadin sIgE as opposed to wheat sIgE, which were positive for those patients (higher specificity). Nonetheless, these 6 patients with negative ω-5 gliadin had wheat sIgE ranging from 0.69 to 48.1 kU_A/L and would have likely been challenged if using the 95% specificity cutoff. Although the sample size is small, these data are

consistent with recent European studies, where component-resolved diagnosis added no additional information in the diagnostic workup of wheat-allergic children [1, 7, 8]; on the other hand, a few earlier studies from Japan found increased diagnostic performance with ω-5 gliadin sIgE when compared to wheat sIgE (Table 2) [6, 9, 10].

Another point of discussion is whether the wheat sIgE/total IgE ratio would improve diagnostic accuracy as potentially suggested with other foods [12]. On the other hand, in one recent study, the component-specific/total IgE ratio did not improve diagnostic performance of Ara h 2 and Cor a 14 in peanut/hazelnut-allergic children [13]. In our cohort, total sIgE was not systematically measured in patients as per food allergy guidelines [14]. We do not exclude, however, that this ratio could potentially improve wheat and ω-5 gliadin sIgE diagnostic performance, and further data are needed.

The strength of our study is that all patients underwent standardized OFC based on PRACTALL guidelines, and a positive diagnosis was confirmed by OFC rather than suggestive clinical history as in some other cohorts (Table 2). In addition, a significant proportion of children challenged had high wheat sIgE levels (n = 25/50 with wheat sIgE above 20 kU_A/L). On the other hand, limitations include missing ω-5 gliadin data for some patients and a relatively small sample size.

All in all, these findings suggest a high positive decision point for wheat sIgE (78.1 kU_A/L). This reinforces the importance of considering OFC in children with IgE-mediated wheat allergy to confirm diagnosis even in patients with relatively high wheat sIgE values, as there is a risk of falsely mislabeling these patients as allergic. The decision to perform OFC and cutoff used should always take into account a risk/benefit assessment including clinical evaluation and OFC setting, since, as in any food challenge, severe reactions can occur. Prospective studies with a larger number of patients are needed to provide additional data on the utility of wheat sIgE and ω-5 gliadin for the diagnosis of IgE-mediated wheat allergy.

Statement of Ethics

The study protocol was approved by the institute's committee on human research.

Disclosure Statement

Prof. Philippe Eigenmann received honoraria and research support from Thermo Fisher. All other authors have no conflicts of interest to declare.

Table 2. Predictive values of wheat and ω-5 gliadin sIgE in children with IgE-mediated reactions: a review of the literature

Study	Year	Country	Age (range), years[b]	WA, *n*	nWA, *n*	sIgE WA[b], kU_A/L	sIgE nWA[b], kU_A/L	ω5g WA[b], kU_A/L	ω5g nWA[b], kU_A/L	Wheat ODP, kU_A/L	Wheat Sp 95%, kU_A/L	Wheat Sn 95%, kU_A/L	ω5g Sp 95%, kU_A/L	ω5g Sn 95%, kU_A/L	AUC wheat, %	AUC ω5g, %
Sampson [2]	2001	USA	3.8 (0.25–14)	17	5						26[c]					
Perry et al. [3]	2004	USA	4.2	15	31	19.6	4.6									
Ito et al. [9][a]	2008	Japan	3.4[d] (1–8.7)	21	14	33.8	7.2			12.5					76.9	85.7
Komata et al.* [11][a]	2009	Japan	1.3[d] (0.5–14.6)	65	236	4.31	<0.35									
Shibata et al. [6]	2011	Japan	2.48[d] (0.6–8.8)	63	21	21.18[d]	14.39[d]	2.04[d]	0.40[d]	15.7	74.5		1.06		62.9	83.3
Ebisawa et al.* [10][a]	2012	Japan	2.3 (0.5–20.4)	137	78	18.1	5.2	1.2	<0.35	10.1					73	78.5
Mäkelä et al. [8]	2014	Finland	1.5 (0.6–17.3)	30	81	18.23	0.25			10.5					87.4	
Nilsson et al. [7][a]	2015	Sweden	5 (1–17)	32	31						70	8	1.3	None	91	78

AUC, area under the curve; *n*, number of patients; WA, Wheat allergy; nWA, non-wheat allergy; ODP, optimal decision point; sIgE, specific IgE; Sn 95%, 95% sensitivity; Sp 95%, 95% specificity; ω5g, omega-5 gliadin.

* From the same center.

[a] Mix of OFC and clinical history for specific IgE.

[b] Expressed as the median, unless specified.

[c] 92% specificity.

[d] Mean value.

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Author Contributions

F.G. contributed to the design of the research, submitted the research to the institute's committee on human research, collected the data, contributed to the analysis of the results and to the writing of the manuscript. J.C.C., S.R., D.S., and P.A.E. contributed to the design of the research, to the analysis of the results, and to the writing of the manuscript.

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