



Clinical thresholds to egg, hazelnut, milk and peanut: results from a single-center study using standardized challenges

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ABSTRACT

Background: Large studies of individual thresholds and risk profiles for foods are sparse. Previous reports indicate that thresholds adjusted for the protein content in foods would be comparable.

Objective: To establish and compare clinical threshold values for egg, hazelnut, milk and peanut, and correlating them to severity of symptoms.

Methods: Seven hundred eighty-one challenges were performed in 487 patients (age range, 0.5–73.5 years). Using interval censoring survival analysis, the dose distribution of thresholds was fitted to a log-normal function. Symptom score was correlated to thresholds.

Results: Based on the 405 challenges resulting in objective signs, similar distribution of thresholds for hazelnut, milk, and peanut challenges were found, whereas individuals with egg allergy were bimodally distributed with a high or a low threshold. Eliciting dose in 10% (95% confidence interval) was 42.9 (24–76.8) mg whole eggs, 133.8 (95.9–186.6) mg whole hazelnut, 106.5 (59.7–190.6) mg roasted peanut, and 2.9 (1.5–5.4) mL milk. Adults showed more severe symptoms and signs than children, and peanut caused more severe reactions than the 3 other foods.

Conclusion: Thresholds for the different foods were not comparable, and eliciting dose for the 4 foods differed, even if adjusted for protein content. Increasing age but not a low threshold dose is associated with severe symptoms on challenge. Peanuts elicit more severe reactions than the other foods.

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Introduction

Total avoidance is at the moment the only effective method to prevent adverse reactions to allergenic foods. This requires correct labeling of products and prevention of unintentional cross-contamination during production and processing. Correctly defined clinical threshold values are prerequisites for regulatory authorities conducting risk assessment and for offering guidelines to the food industry. Equally important, the knowledge of a personal threshold allows patients, caretakers, and physicians to estimate an individual risk level and to devise a strategy for proper avoidance.

For *individuals*, the “true” threshold in a titrated challenge procedure lies between the no observed adverse effect level, defined as highest amount of the allergenic food not eliciting any allergic reaction, and the lowest observed adverse effect level (LOAEL), representing the lowest amount of the food eliciting allergic symptoms.¹ Individual LOAELs are encumbered with a high degree of variation,^{2–9} and especially the definitions of the challenge-termi-

nating stop-criteria are ambiguous and poorly defined in most centers.

Population-based risk assessment deals with the amount of food eliciting reactions in a certain fraction of a food-allergic population, such as the eliciting dose in 10% (ED₁₀). Performing challenges in all food-allergic patients is impossible; therefore, statistical models based on individual LOAELs have been developed for the construction of a dose–response curve for a given allergen.^{10,11} Only a few studies have compared thresholds between different foods, in other words, whether different foods display different thresholds under similar challenge conditions, practical procedures, and identical inclusion criteria.^{6,12} These have shown that identical amounts of milk, peanut, and egg elicited reactions in different fractions of milk-, peanut-, and egg-allergic patients. In a review study by Bindslev-Jensen et al,¹⁰ previously published thresholds of egg, milk, and peanut were compared; a key observation was that protein (allergen) content had a confounding effect on observed thresholds and should be standardized when comparing foods. If so, this would only simplify labeling and legislation, because threshold, adjusted for protein (allergen) content, would be comparable. This finding has never been confirmed.

The relationship between thresholds and symptoms, both concerning historical symptoms by accidental intake and signs elicited by challenge in a controlled setting, remains inconclusive. Patients with a history of severe reactions have been shown to have lower

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threshold by some⁴ but not by other investigators,¹³ whereas data from challenges show little or no correlation between thresholds and symptom severity.¹⁴ Whether less sensitive patients with high thresholds may develop severe symptoms, or whether these would only occur in more sensitive patients, is unclear.

The aim of this retrospective chart review study was to establish and compare clinical threshold values for the most prevalent allergens in our area (egg, hazelnut, milk, and peanut), and correlate them to severity of symptoms.

Methods

Data from all consecutive patients, investigated for egg, hazelnut, milk, and peanut allergy, that is, referred with a positive case history ranging from mild to very severe reactions, during the period from March 2003 to March 2009 at the Allergy Centre, Odense University Hospital, Denmark, were retrospectively evaluated. Final inclusion criterion was a positive or negative oral challenge with the offending food. In case of repetitive challenges in a patient, the initial challenge was used, whereas patients with multiple challenge–confirmed food allergies were included with challenge data for each relevant food. All patients gave informed consent and were evaluated according to routine standards in the department as previously described.¹⁵

Challenges

All patients were challenged according to European Academy of Allergy and Clinical Immunology guidelines¹⁶ by trained staff. Children younger than 4 years of age were exposed to foods by open food challenge (OFC), whereas the double-blind, placebo-controlled food challenge (DBPCFC) was planned over 2 separate days in all participants 4 years of age or older. Because of compliance problems, DBPCFC was substituted by OFC in 284 patients 4 years of age or older. Challenges were performed with commercially available pasteurized whole egg (fluid mixture of egg white and yolk), pasteurized low-fat milk (fat content 1.5%), whole raw dried hazelnuts, and whole roasted unsalted peanuts. Blinding formulae and administered dosages of the culprit food are presented in Table 1. Deviance from this dosage scheme because of repeating a dose, deferring the next dose, or insertion of an extra dose could occur. Vehicle foods were used as placebo reference in DBPCFC. Stop criteria for all challenges were development of systemic objective signs (group 2 or higher; see later discussion), whereas subjective symptoms (group 1) only were accepted as stop criteria in cases in which subjective symptoms were reported and patients either refused further participation or no objective signs appeared after

administration of a full dose. Symptoms and signs appearing after a challenge were classified into 5 groups according to Sampson et al.¹⁷ Group 1 included subjective symptoms (nausea, abdominal pain, pruritus, oral allergy syndrome [OAS]) and localized urticaria; group 2: generalized urticaria, angioedema, and emesis; group 3: repetitive vomiting and rhinorrhea; group 4: diarrhea and asthma; and group 5: denoted anaphylactic shock.

Statistics

A cumulative distribution function, plotting cumulative number of reacting patients against log dose, was used to model dose–response data. Using interval censoring survival analysis, the dose distribution of thresholds was fitted to a log-normal function.^{1,18} Confidence intervals were calculated and added. Threshold was correlated to allergen, age and sex of patients, type of food, and type of challenge (OFC vs DBPCFC) using multiple regression. Symptom grading was correlated to threshold, age and sex of patients, type of food, and type of challenge using ordinal logistic regression. All calculations were performed in Stata version 10 (Stata corp, College Station, Texas) on a Windows 7 platform.

Results

A total of 487 patients with 781 performed challenges entered the study. Most were children; 48% of patients were younger than 4 years of age, and 90% were younger than 15 years of age. Patients challenged with egg were significantly younger than those challenged with hazelnut ($P = .002$) and peanut ($P = .02$). Patients positive to hazelnut were significantly older compared with patients reacting to the 3 other allergens ($P < .05$). Sex ratio (m/f) was 1.8, and no placebo reactions during DBPCFC occurred. Four hundred five of the 781 performed challenges (51%) elicited objective signs; 44 (5%) showed only subjective symptoms.

Thresholds

First-dose responders, that is, patients reacting to the initial administered dose, were observed for all 4 foods. LOAEL is therefore similar to or lower than the first administered dose; see Table 2. All 30 first-dose responders reacted with objective signs. The frequency of first-dose responders in challenges with egg, hazelnut, and peanut was 5 to 8%, significantly lower ($P = .0012$) than the 21% reacting to the first dose of milk (Table 2).

Thresholds related to subjective symptoms only ($n = 44$) were excluded in the statistical model for estimating threshold distributions. In the remaining 405 challenges related to objective signs,

Table 1
Dosage scheme for performed challenges

	OFC				DBPCFC ^a			
	Egg (mg)	Milk (ml)	Hazelnut (mg)	Peanut (mg)	Egg (mg)	Milk (ml)	Hazelnut (mg)	Peanut (mg)
Dose no.								
1	11	5	1	1	5	5	85	85
2	44	10	10	10	50	10	170	170
3	250	20	100	100	250	40	690	690
4	500	40	200	200	500	80	1,380	1,380
5	1,000	80	700	700	1,000	160	2,750	2,750
6	2,500	160	1,300	1,300	2,500		5,500	5,500
7	5,000		2,600	2,600	5,000		14,500	14,500
8	40,700		5,100	5,100	40,000			
Total	50 g	315 ml	10 g	10 g	50 g	295 ml	25 g	25 g
Masked in	Chocolate drink				Chocolate bar			
Containing	Oat flour, sugar, chocolate, vanilla aroma				Margarine, dark chocolate, salt, icing sugar, oat grains, oat flour, mint			

Abbreviations: OFC, open food challenge; DBPCFC, Double-blinded placebo-controlled food challenge.

^aPresented as mg/ml culprit food without matrix.

Table 2
Characterization of study population and performed challenges

	Total	Egg	Hazelnut	Peanut	Milk
Patient age (Mean [range])	7.5 [0.5–73.5]	6.0 (0.9–65.2)	9.1 [1.1–67.9]	7.8 [1.1–73.5]	7.9 [0.5–63.0]
Challenges performed	781	237	174	249	121
OFC	663	215	145	204	99
DBPCFC	118	22	29	45	22
No. positive outcome (% of performed challenges)	449 (57%)	164 (69%)	72 (41%)	165 (66%)	48 (40%)
Objective signs	405	155	59	149	42
Only subjective symptoms ^a	44	9	13	16	6
No. first-dose responders	30	8	5	8	9
% of pos. Obj. Chal.	7%	5%	8%	5%	21%
LOAEL	—	5 mg	1 mg	1 mg	5 mL
Protein content (%)	—	12.5 %	14.9 %	24.6 %	3.5 %

Abbreviations: OFC, open food challenge; DBPCFC, double-blinded placebo-controlled food challenge; LOAEL, lower observed adverse effect level.

^aSubjective symptoms included oral allergy syndrome, nausea, abdominal pain, and pruritus.

individual LOAELs were only affected by the type of allergen ($P < .0001$), but neither by age ($P = .10$) nor by the sex ($P = .88$) of the patients, when adjusted for each other. The thresholds for each of these patients were used to estimate and plot the distribution against cumulative frequency (Fig 1). By comparing the tangential slopes for each allergen at ED_{50} , in other words, the threshold-eliciting reactions in 50%, we found that hazelnut, peanut, and milk follow the same course, whereas thresholds of egg-allergic patients are bimodally distributed, with a higher proportion of patients either having a high or a low threshold.

The dose of culprit food (mg egg, hazelnut, and peanut, and mL milk) necessary to elicit reactions in 5% or 10% (ED_{05} or ED_{10}) for these 4 food-allergic populations is presented in Table 3. Additionally, ED_{05} and ED_{10} are presented in milligrams protein. Adjusted for protein content, milk had a significantly higher ED_{05} and ED_{10} than the 3 other allergens ($P < .05$), whereas egg had a significantly lower ED_{05} than the 3 other allergens ($P < .05$).

Symptoms

Objective signs were seen in 405 or 90% of the 449 positive challenges, and 213 of these reported additionally subjective symptoms. Most (150 patients) reported subjective symptoms at a lower dose than the 1 eliciting objective signs, the remaining (63 patients) at the same dose. Subjective symptoms, such as OAS and abdominal pain, without any objective signs, were reported in 44 cases. Most (89%) of all 449 reactions during challenge were mild (groups 1–3), classified according to Sampson.¹⁷ No very severe reactions (group 5) were observed.

Patient age was stratified into 3 groups; younger than 4 years ($n = 238$); 4 to 14 years ($n = 188$), and 15 years or older ($n = 23$). Age affected severity of symptoms, both crude ($P = .001$) and adjusted for thresholds, sex, and food type ($P = .011$). Age 15 years or older increased the risk of severe symptoms (OR [95% confidence interval] = 1.89 [1.33–2.68], $P = .001$; Fig 2A) compared with affiliation to 1 of the 2 younger groups. Patients challenged with peanut had significantly more severe symptoms compared with the 3 other foods (OR = 1.94 [1.30–2.90]; $P = .001$; see Fig 2B). Symptom score was unaffected by threshold, sex of patients, and type of challenge (OFC/DBPCFC). The type of challenges did not influence the frequency of subjective symptoms in the group 15 years and older.

Discussion

This study is the largest published study with threshold values from multiple food allergens obtained in a single center. By plotting the cumulative frequency of thresholds (Fig 1), we were able to compare the distribution of thresholds from different allergens. Only 2 studies have presented data on threshold to more than 1 food.^{6,12} Our findings are in agreement with these 2 studies; that milk-allergic patients have lower thresholds, measured in milliliters, than that of egg- and peanut-allergic patients, which is measured in milligrams. This tendency was also found previously in a meta-analysis using challenge data from 203 individual challenges obtained from 9 different studies.¹⁰ The differences between allergenic foods could be neglected if protein contents were compared instead of the amount of the culprit food. Adjusting for protein

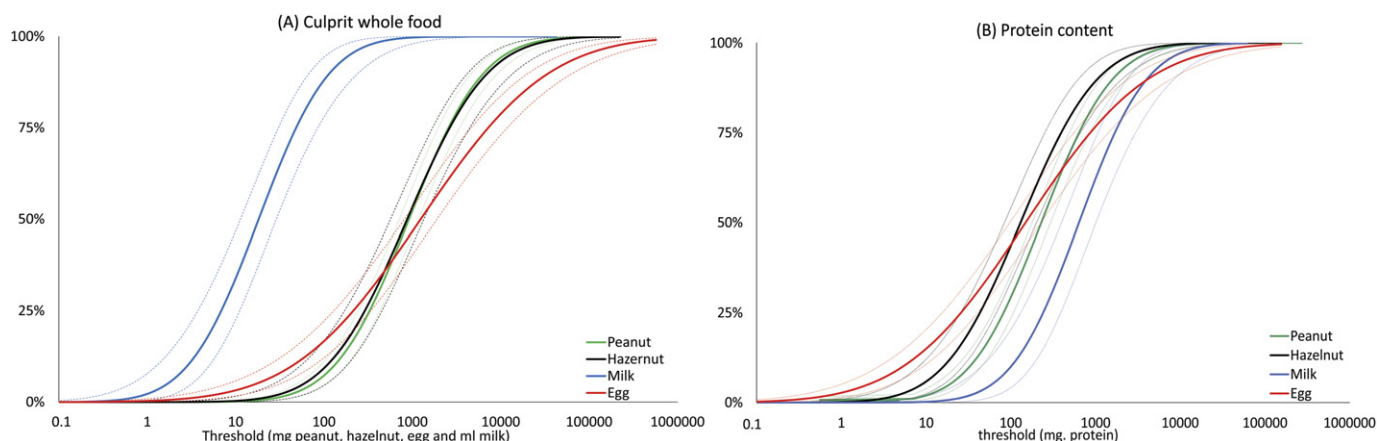


Fig. 1. Cumulative distribution (%) of objective threshold in an estimated population of food-allergic individuals with 95% CI (dashed lines). Individual thresholds from actual challenges, underlying the model, are marked with a cross. Thresholds are presented as culprit food: peanut (mg), hazelnut (mg), egg (mg), and milk (mL) (A), and in milligrams protein (B).

Table 3Estimated eliciting dose (+/– 95% CI) causing objective signs in 5% and 10% of a food allergic population (ED₀₅ and ED₁₀)

	Egg		Hazelnut		Peanut		Milk	
	mg	95% CI	mg	95% CI	mg	95% CI	mL	95% CI
Whole food								
ED ₁₀	42.9	(24–76.8)	106.5	(59.7–190.6)	133.8	(95.9–186.6)	2.9	(1.5–5.4)
ED ₀₅	16.6	(8.8–32)	58.1	(30.2–112.8)	77.0	(52.8–112.2)	1.7	(0.8–3.1)
Protein								
ED ₁₀	5.36	(3.0–9.6)	15.9	(8.9–28.4)	32.9	(23.6–45.9)	100.2	(52.7–190.5)
ED ₀₅	2.08	(1.1–4.0)	8.7	(4.5–16.8)	18.9	(13.0–27.6)	59.3	(29.1–109.9)

Presented as amount whole food (mg egg/hazelnut/peanut and mL milk) and mg protein.

content in this study as shown in Figure 1B did not, however, remove the differences in threshold distribution between the 4 foods. Thresholds of hazelnut, milk, and peanut seem to be similarly distributed, with few patients having either a high or low threshold. In contrast, individuals with egg allergy are more equally scattered over the dose range. No obvious explanation why threshold to egg deviates from the other allergens was found, although the same result was found previously by Moneret-Vautrin et al.¹² Stratification of egg thresholds based on age, symptoms, and year of challenge, such as 2003–2005 vs 2007–2009, did not reveal any difference (data not shown).

Symptoms

Early reports have indicated a poor correlation between thresholds and symptoms/signs, elicited during challenge.¹⁴ This was confirmed by our study ($P = .47$). We found that adults (≥ 15 years) have more severe symptoms than patients younger than 15 years. Furthermore, adverse reactions after peanut ingestion are more severe than after ingestion of other foods, supporting previous findings.¹⁹ Two studies have shown inconclusive results concerning the relationship between peanut threshold and severity of symptoms estimated from case history. Wensing et al.⁴ reported that patients with a history of severe symptoms had a lower threshold, whereas Taylor et al.¹³ found no correlation between threshold and case history symptoms. The reason for this discrepancy could be that the eliciting doses in historical reactions are often doubtful or unclear. The correlation between severity of reported accidental reactions and severity of reactions after controlled challenges is poor,²⁰ mainly because titrated controlled challenges are not designed to provoke severe reactions. Severity after ingestion of an offending food is probably not correlated to the absolute amount of ingested food, but rather the relative amount of excess food in

relation to the actual patient's threshold, that is, the distance from the ingested amount of food to the patient's actual threshold.

Eliciting dosage

The most sensitive patients in this study, first-dose responders, had LOAEL eliciting objective signs after ingestion of 5 mg egg, 1 mg hazelnut, 1 mg peanut, and 5 mL milk. A few published studies, based on large number of patients, have previously addressed individual LOAEL, which for egg, peanut, and hazelnut are in comparable range.^{4,6} LOAEL in milk-allergic patients have been reported lower than our findings; 0.1 to 0.5 mL.^{6,9} For milk, egg, and peanut, a lower LOAEL related to subjective symptoms has been reported.^{2,3,5} This substantiates the need for crucial use of strict stop criteria for comparing LOAELs. By using these systemic objective signs, severe reactions as well as placebo reactions can be avoided or at least reduced during challenges.

The dosage eliciting reaction in a certain percentage of the food-allergic population, that is, in 1% or 10% (ED₀₁ or ED₁₀) has previously only been addressed in relation to peanut. In 2 studies, Taylor et al.^{1,13} found ED₁₀ for peanut to be 12.3 (9.0–16.8) mg, which is considerably lower than the 133.8 (95.9–186.6) mg peanut found in our study. ED₀₁ has to be addressed with precaution, if it is based on small sample sizes (<100 patients). An ED₀₁ of 27 (17–42) mg peanut found in this study is therefore only a rough estimate, but still it is considerably higher than the ED₀₁ of 2.7 (0.8–4.5) mg peanut estimated in the meta-analysis by Bindslev-Jensen et al.¹⁰ The high peanut threshold in our study could be attributable to the design of the challenge series and thereby the fraction of first-dose and full-dose responders. In this study DBPCFC starts with 85 mg peanut, a dose considerably higher than in the 1 mg in the OFC and the starting dose in other studies as well (0.1–5 mg).¹³ Of the 7 first-dose responders to peanut, 5 underwent DBP-

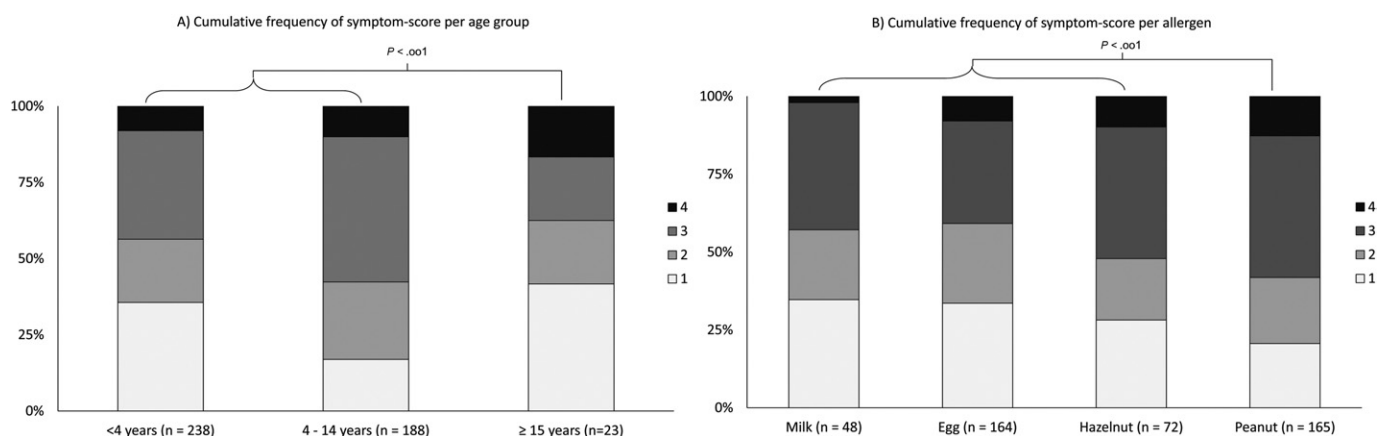


Fig. 2. Cumulative frequency of symptom-score, separated into age groups (A) and allergens (B). Symptoms were scored into 5 groups (17), ranging from localized urticaria, nausea, abdominal pain, pruritus, OAS (group 1), generalized urticaria, angioedema, and emesis (group 2), repetitive vomiting and rhinorrhea (group 3), to diarrhea and asthma (group 4). Group 5 including anaphylaxis did not occur in this study.

CFC, which could influence the overall threshold estimate. Seventeen patients, mainly children, were, however, full-dose responders. Data on full-dose responders from other studies are limited; this illustrates that the challenge regimen has to include adequate amounts of food; that is, it should reflect the amount in a normal meal, to assure positive reactions in less sensitive patients to avoid false negative outcomes and thereby underestimation of ED₁₀.

The high frequency of first-dose responders in milk (19%) is an obstacle. The true threshold of these first-dose responders lies lower than the first administered dose at 5 mL milk, which clearly is too high. This could explain the discrepancy to LOEAL for milk found in other studies,^{6,9} and emphasize the importance of designing low-dose challenges as well, ensuring that all allergic individuals experience symptoms within the challenge interval. Our data have now prompted a change in the routine challenge practice with milk in our center.

For all 4 allergens, most of the challenges ended up being OFC, because 284 DBPCFC was substituted to OFC. This was especially abundant in children aged 4 to 14 years, when some refused participation on 2 days ($n = 57$), and others would not accept the taste of the double-blind challenge material, despite various recipes being used to increase palatability. An open challenge was therefore offered to these patients to obtain the second best available measure, namely, a threshold based on an open challenge.

Conclusion

The distributions of thresholds for the 4 allergens seem to be different, even if adjusted for protein content. Patients allergic to egg are more often really sensitive (low threshold) or have a high threshold, compared with patients allergic to peanut, hazelnut, and milk. Severity of symptoms is not associated with thresholds but with increasing age. Peanuts elicit more severe reactions than the 3 other foods.

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