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The economic effect and outcome of delaying oral food challenges

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ABSTRACT

Background: Food specific IgE (sIgE) is a useful marker to assess predictability of oral food challenge (OFC) outcome. A threshold of less than 2 kUA/L for peanut, egg, and milk has been proposed as a 50% negative predictive value at which patients may pass an OFC.

Objective: To assess the economic effect and outcome of delaying OFCs.

Methods: A retrospective analysis was performed for peanut, egg, and milk OFCs conducted between 2001 and 2012 at a tertiary food allergy referral center. Delayed OFC was defined as greater than 12 months from the time the sIgE level became less than 2 kUA/L. Time to OFC was explored in association with skin prick test result (wheal size), OFC outcome, and the economic effect of delay.

Results: Of 319 challenges, 173 OFCs were delayed (54.2%) by a mean time of 35.5 months (range, 13–123 months) vs a mean time of 4.2 months in the 146 challenges that were not delayed ($P < .001$). The overall OFC passage rate was 89.9%. There was no association between delayed OFC and history of anaphylaxis, type of allergen, age at OFC, or challenge outcome. Delay in OFC was associated with an estimated mean economic cost of \$12,203 per patient (\$4,184 per 12 months) and \$1,951,487 total (total delay, 5,597 months) in this population.

Conclusions: Despite a 50% negative predictive value, more than 50% of OFCs were delayed in this population by a mean time of nearly 3 years. Delaying OFC is associated with increased costs, and quality improvement is needed to help decrease time to OFC and reduce the economic burden of food allergy on families and the health care system.

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Introduction

Food allergy affects 8% of children in the United States based on self-report survey.¹ Several studies report an overall increase in food allergy prevalence, although exact US prevalence data and trend interpretation are limited based on use of indirect methods and not oral food challenge (OFC) to confirm allergy.^{2–4} However, according to most available estimates, there appears to be an increase in children with a diagnosis of food allergy.⁵ Inappropriate

testing, especially using food specific IgE (sIgE) alone, in patients without a convincing history of suspected food-induced allergic reaction may be contributing to misdiagnosis, unnecessary food avoidance, and inflated estimates of food allergy prevalence.^{6,7}

The gold standard diagnostic procedure for suspected IgE-mediated food allergies is the double-blind, placebo-controlled food challenge.⁵ In clinical practice, open (nonmasked) challenges are well accepted as an alternative and are preferentially used because they are less labor intensive, more time efficient, and more practical.⁸ Skin prick testing (SPT) and sIgE have been identified as useful markers to predict OFC outcome. An sIgE threshold of less than 2 kUA/L to peanut, egg, and milk has been proposed as a 50% negative predictive value (NPV) at which patients can be expected to pass an OFC and a challenge procedure can be safely offered.⁹

There is sparse literature exploring why OFC may not be offered or if offered why it may be deferred. Reasons may include conflicting allergy testing data, the patient has a history of severe anaphylaxis or poor asthma control, or deferral may simply be due to patient, caregiver, or clinician preference.¹⁰ On the basis of survey

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report, allergists may decide to delay or defer an OFC due to concerns that the patient may react, time limitations to perform the OFC, poor reimbursement, inadequate training, lack of comfort in performing the challenge, or lack of resources (staff, space) to perform the OFC.¹¹ The most common reasons for deferring OFC according to a recent caregiver survey were “no interest in adding the food into the diet” and “fear of not passing the challenge.”¹²

Food allergy was recently estimated to have a direct annual medical cost of \$4,184 per year per child (inclusive of direct medical, out-of-pocket, lost labor productivity, and related opportunity costs), with nearly 80% of these costs being borne by the family and just 20% being related to direct medical care.¹³ It is possible that delaying or deferring the OFC, despite the patient being an appropriate OFC candidate, may lead to additional unnecessary financial costs (eg, opportunity costs, lost-labor productivity costs), as well as the opportunity cost of not potentially being able to reintroduce the food.¹³ Although the reasons for delaying an OFC procedure are complex and dependent on the allergist's assessment and the caregiver and patient or family preference for the procedure, the costs associated with OFC delay should be considered. No study to date has explored the health or economic effect of delaying the decision to perform OFC. The objectives of this study were therefore to investigate the timing of OFC administration in relation to testing results, the OFC outcome, and the economic cost of delaying the OFC.

Methods

Study Design

This was a retrospective analysis of peanut, egg, and milk open OFCs conducted at clinics at the Division of Allergy and Clinical Immunology, University of Michigan, between 2001 and 2012. These 3 foods were chosen based on prior divisional study identifying them as the most common OFCs offered and because these items have previously been evaluated and proposed as having a 50% NPV for reactivity.^{9,14} Patients who underwent OFCs were identified from the Division of Allergy and Clinical Immunology database using *International Classification Diseases, Ninth Revision (ICD-9)*, coding, *Current Procedural Terminology (CPT)* coding for ingestion challenge, and medical record review for OFC procedures performed. Patients who had peanut, egg, and milk SPTs and corresponding food sIgE tests before challenge were included in the analysis. Patients with a history of non-IgE-mediated food allergy were excluded.

Delayed OFC was defined as an OFC that occurred more than 12 months from the time when the patient's sIgE level was less than 2 kUA/L (50% NPV) for peanut, milk, or egg. Variables that were investigated include time (months) to OFC, number of visits with allergy testing once the sIgE level decreased to less than 2 kUA/L, SPT result (wheal size), and OFC outcome. Total costs associated with delay were calculated according to recently published data quantifying the direct and indirect economic effect of food allergy.¹³ The study was approved by the University of Michigan Institutional Review Board.

Statistical Analysis

The primary outcome was to investigate the proportion of delayed OFCs and compare elapsed time between the delayed group and the nondelayed group. Secondary outcome measurements included differences in OFC outcome, SPT result (wheal size), age at OFC, number of additional visits, history of anaphylaxis, and allergen type between the 2 groups. Descriptive statistics were determined through frequency analysis. Mean differences between groups were assessed using independent sample *t* tests and proportional differences by Fisher exact tests. Predictive associations

were determined through both logistic regression and linear regression. An α of .05 was used for significance. The study had 80% power to detect a 20% difference in all primary and secondary outcomes between the groups with 62 patients per arm. All analyses were performed using STATA SE, version 13 (StataCorp, College Station, Texas).

Results

There were 270 patients identified who underwent 319 OFCs to peanut, milk, or egg between 2001 and 2012. Forty-five patients underwent 2 or more challenges. Patient characteristics are listed in Table 1. The mean age at food allergy diagnosis was 27 months, and the mean age at initial OFC was 80 months. OFC to egg was performed most frequently, followed by OFC to peanut and milk. Table 2 lists the presenting symptoms of food allergy within this population. Hives were the most commonly reported symptoms of presenting illness. There were 229 challenges (71.8%) performed in patients who had a prior history of at least a single presenting symptom to the challenged food, whereas 73 (22.9%) were performed in patients avoiding the food item due to sensitization (eg, a high sIgE level or large wheal on skin testing), and 17 (5.3%) were performed in patients avoiding the food secondary to potential cross-reactivity with another food allergen. Overall, 56 (17.6%) of 319 challenges were to foods in patients with medical record-verified symptoms that were consistent with anaphylaxis, according to the 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network criteria. There was no association noted between the OFC item and a reported history of anaphylaxis.

Of 319 OFCs, 173 (54.2%) were delayed, defined as occurring more than 12 months from the time that the food sIgE level decreased to less than 2 kUA/L (Table 2). Mean age at the time of the OFC was 88 months in the delayed group vs 72 months in nondelayed group ($P \leq .001$). The mean time to OFC was 35.5 months (range, 13–123 months) in the delayed group vs 4.2 months in the nondelayed group ($P < .001$). Peanut was the most frequently delayed type of OFC ($n = 74$) (Fig 1) and was delayed the most number of months (mean of 37 months in the delayed group) (Fig 2). These patients were also the oldest at the time of the OFC (mean age, 88 months). The mean number of additional visits with testing after the sIgE level decreased to less than 2 kUA/L in the delayed group was 2.13 (range, 1–7). Egg OFC was associated with the most number of visits with testing in the delayed group (mean, 2.29). Combined OFC passage rate for all items was 89.9%, with 83.7% passing peanut OFC, 93.1% egg OFC, and 95.4% milk OFC. The odds of passing either a milk (odds ratio) [OR], 4.01; 95% confidence interval [CI, 1.1–14.1; $P = .03$] or egg (OR, 2.9; 95% CI, 1.25–7; $P = .01$) OFC were significantly higher than passing a peanut OFC. The passage rate for delayed OFC was 92.5% vs 87.6% for nondelayed OFC, which was not significant. Peanut OFC had the lowest pass rates in both the delayed and nondelayed OFC groups compared with egg and milk.

Table 1
Study Population Characteristics

Characteristic	Finding (N = 270)
Male, No. (%)	174 (64)
Multiple food allergies, No. (%)	180 (67)
Comorbid atopic disease, No. (%)	
Atopic dermatitis	147 (54)
Allergic rhinitis	132 (49)
Asthma	93 (34)
Mean age at initial food allergy diagnosis, mo	27
Mean age at initial oral food challenge, mo	80

Table 2
Presenting Symptoms at Initial Food Allergy Diagnosis in 319 OFCs

Symptom	Total No.	Delayed OFC, No. (%)	Nondelayed OFC, No. (%)
Any symptom at presentation	229	112 (49)	117 (51)
Anaphylaxis	4	2 (50)	2 (50)
Hives	151	76 (50)	75 (50)
Worsening atopic dermatitis	19	12 (63)	7 (37)
Facial swelling	42	18 (43)	24 (57)
Vomiting	46	24 (52)	22 (48)
Any respiratory symptom (cough, wheeze, dyspnea)	25	10 (40)	15 (60)
No symptoms, avoiding because of positive test result	73	51 (70)	22 (30)
Avoiding because of other food allergy (cross-reactivity)	17	10 (59)	7 (41)

Abbreviation: OFC, oral food challenge.

Possible explanations for delayed OFC were explored, including the patient age at the time their sIgE level became less than 2 kUA/L (50% NPV), having a recent positive SPT result (≥ 3 -mm wheal) before challenge, and other miscellaneous potential predictors, including age of one's food allergy onset, undergoing multiple challenges and having to prioritize the ordering of which food to offer OFC, a history of a severe reaction to the food allergen, and having only food sensitization to the item (without a history of actual ingestion being attributable to causing symptoms). Table 3 details features of the challenges, comparatively, stratified by delay vs no delay. The mean patient age when the sIgE level reached the 50% NPV was 52 months in the delayed OFC group vs 66 months in the nondelayed OFC group ($P = .003$). Only 66 (38.2%) of 173 had a positive SPT result within 12 months of their OFC and 33 (19.1%) of 173 within 13 to 24 months of their OFC among all individuals within the delayed OFC subgroup (data not shown). Of the 45 patients who underwent 2 or more challenges, 18 patients underwent at least one OFC that was not delayed (38 total appropriately timed OFCs performed in this subgroup), which thus accounts for only 20 OFCs that were delayed due to possible prioritization of one food over another. OFC delay was significantly associated with having isolated food sensitization to the allergen without clinical reactivity (OR, 2.12; 95% CI, 1.2–3.7; $P = .007$). Past reported anaphylaxis to the item was not significantly associated with delayed OFC. Furthermore, delay in OFC was not significantly associated with allergen type, patient age at food allergy diagnosis, or the age of the patient at the time of the most severe reaction to that allergen.

Table 4 summarizes the SPT and sIgE results for all challenges. Within this population, most of the challenges were performed in patients when the sIgE level was less than 2 kUA/L (286 [89.6%] of 319). Mean SPT wheal size nearest the time of the OFC was surprisingly larger among nondelayed OFCs (2.85 mm) than delayed OFCs (2.35 mm) across all items challenged, as well for each of the food items. Among delayed OFCs there were only

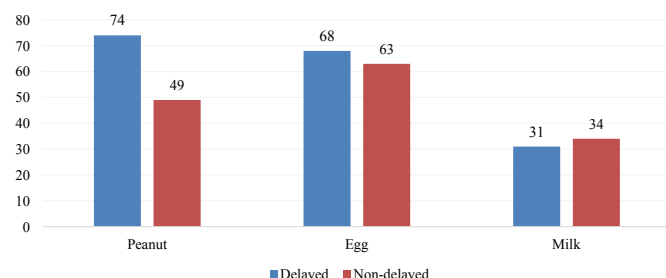


Figure 1. Breakdown of number of delayed and non-delayed challenges, by allergen type (n = 319).

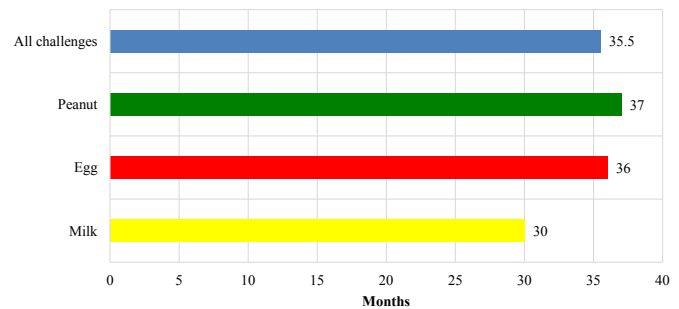


Figure 2. Mean time to challenge by allergen, among delayed oral food challenges.

12 challenges with SPT wheal size above the published 95% positive predictive values (PPVs) (egg white, ≥ 7 mm; milk, ≥ 8 mm; peanut, ≥ 8 mm), and the pass rate for these was 83%.¹⁵ There were 123 challenges performed in patients with both negative SPT and sIgE results near the time of OFC (55 to peanut, 44 to egg, 24 to milk), and 74 (60%) of the 123 challenges were delayed (data not shown).

Delay in OFC was associated with an estimated mean economic cost of \$12,203 per patient per allergen in this population. This was calculated using estimated direct and indirect costs of living with food allergy of \$4,184 per patient per year, as determined by Gupta et al, applied to our findings of mean OFC delay of 35 months (2.92 years). This estimate is adjusted to exclude failed challenges within the delayed group (n = 13). Combining figures for all delayed OFCs, which comprised a total of 5,597 months, delay in OFC amounted to an estimated total cost of \$1,951,487 within this population in our center alone among this group.

Discussion

In this food allergic population more than half (173 of 319) of OFCs to peanut, egg, and milk were delayed by more than 12 months after the sIgE level decreased below 2 kUA/L, a level associated with a strong likelihood of passing. We used an a priori cutoff to define delay as the patient not undergoing challenge within 12 months of their sIgE level eclipsing the 50% NPV level per

Table 3
Time Delay to Performing OFCs

Variable	Total	Delayed OFC	Nondelayed OFC	P
All challenges, No. (%)	319	173 (54)	146 (46)	
Peanut	123	74 (60)	49 (40)	
Egg	131	68 (52)	63 (48)	
Milk	65	31 (48)	34 (52)	
Mean time to OFC from sIgE level <2 kUA/L, mo	21	35.5	4.2	<.001
Peanut	24	37	5	
Egg	21	36	4	
Milk	16	30	4	
Mean age at time of OFC, mo	80	88	72	<.001
Peanut	88	95	78	
Egg	81	84	78	
Milk	64	77	52	
Mean age at time of sIgE level <2 kUA/L, mo	58	52	66	.003
Peanut	63	58	71	
Egg	58	49	74	
Milk	47	47	47	
Mean No. of additional visits with testing	1.22	2.13	0.14	
Peanut	1.33	2.05	0.22	
Egg	1.24	2.29	0.10	
Milk	1.00	1.97	0.12	

Abbreviation: OFC, oral food challenge.

Table 4

Food-Specific Testing Characteristics Near Time of OFC

Challenge	SPT Wheal Size, Mean (Range), mm	slgE, Mean (Range), kUA/L	OFC With slgE <2 kUA/L, No.	OFC With slgE of 2–5 kUA/L, No.	OFC With slgE >5 kUA/L, No.
All challenges	2.57 (0–18)	1.16 (0–36)	286	22	11
Delayed	2.35	0.58	168	5	0
Nondelayed	2.85	1.85	118	17	11
Peanut	1.88 (0–13)	0.99 (0–36)	112	10	1
Delayed	1.87	1.53	69	5	0
Nondelayed	1.90	0.63	43	5	1
Egg	3.03 (0–11)	1.31 (0–16)	113	12	6
Delayed	2.72	0.57	68	0	0
Nondelayed	3.38	2.12	45	12	6
Milk	2.89 (0–18)	1.18 (0–17)	61	0	4
Delayed	2.69	0.51	30	0	0
Nondelayed	3.07	1.80	30	0	4

Abbreviations: OFC, oral food challenge; slgE, specific IgE; SPT, skin prick test.

allergen. Although arbitrary, we consider 12 months to be a fairly conservative and feasible timeframe to allow for scheduling and logistical coordination of the procedure if there was intent by the practitioner or the patient or family to act on the test result. The field lacks specific recommendations regarding the optimal timing of when to perform the OFC in relation to favorable testing results, and the 50% NPVs established by Perry et al⁹ remains one of the few described possible outcome points in the literature.^{5,9,15} In our population, this seems to have been an ideal performance point for established safety, delay notwithstanding. However, there has not been any study to our knowledge that has looked at the use and outcomes of these decision points and assessed their feasibility as a defined OFC metric.

This study addresses multiple different associations with delay in OFC, including duration of the delay and whether the delay was related to OFC outcome or direct economic costs. In the subgroup of patients ($n = 45$) who underwent 2 or more OFCs, we did not find a significant number of challenges that were delayed ($n = 20$) because of possible prioritization of one food over another for OFC. However, given that separate OFCs to 2 different foods could be performed within just a few days, the effect of prioritizing one food over another should be quite minimal if the practitioner or family were motivated to undergo the procedure. Another possible explanation for the extent of delay we explored was an association with having persistently positive SPT results despite an slgE level at or below the 50% NPV. There is no clear guidance on which measure of testing is the better predictor of outcome and should govern when there is discrepancy between the SPT and slgE test results. In our population, 39.9% of challenges in the delayed group had a positive skin test result (>3 mm) within 12 months of the challenge and only 20.2% within 13 to 24 months of OFC. However, this proportion with a positive skin test result within 1 to 2 years of the slgE level decreasing below 2 kUA/L was much lower than we anticipated given the extent of the delay in this population and likely not the most attributable factor to fully account for the delay. We did not find a significant number of delayed challenges with recent SPT wheal size above the published 95% PPV ($n = 12$).

Another possible explanation for the delay was the child's age at the time of their slgE level becoming less than 2 kUA/L (50% NPV). We found that the patients were significantly younger at the time of reaching the 50% NPV (52 months or 4.3 years) in the delayed vs nondelayed group (66 months or 5.5 years), which may suggest a more prominent role for an age bias explaining the delay noted. There are no specific recommendations regarding age at the time of the OFC, but it may be delayed by the mutual decision of both parent and practitioner in infants and young children because of the perception that the child will be poorly cooperative during the

procedure or unable to verbalize symptoms.^{5,8} In practice, OFC is routinely performed in children younger than 5 years, and no firm guideline has established a lower limit below which challenge should be offered.

A recent study by Davis et al¹² explored parentally reported reasons associated with delay in OFC, which noted fear of adverse outcome, doubt the child would incorporate the food into the diet afterward, or lack of importance or low prioritization to reincorporate the food as major reasons for deferral but did not note the child's age as a barrier. Moreover, more recent data may refute that there is a true lower age limit where challenge is unsafe or infeasible to attempt. Investigators in the Learning Early About Peanut (LEAP) study successfully performed 271 challenges in children between the ages of 4 and 11 months, with only 7 mild adverse events, demonstrating that challenge in very young children is safe and feasible.¹⁶ Similar data were found in the Australian HealthNuts cohort, where investigators challenged several hundred 12- to 16-month-old children.¹⁷ Both the LEAP and HealthNuts experience should provide some measure of reassurance that office-based OFC in young children is logistically feasible or practical and seemingly as safe as OFC in older children. In both studies there were low published rates of severe reactions, most of which were mild and cutaneous, with urticaria as the predominant feature.^{16,17} This collective experience would refute that there is an age at which someone is too young to undergo OFC and that there may be considerable practitioner bias influencing such a notion.

Most prominently, our study highlights that OFC delay is associated with rather significant economic effects at the patient and health care system levels. This is the first such study to quantify economic outcomes associated with delay in OFC. Gupta et al¹³ reported an estimated total economic cost of food allergy at \$4,184 per year per child, which includes the direct medical costs of food allergy to the US health care system (outpatient physician office visits, emergency department visits, and hospitalizations), as well as the direct and indirect costs borne by the family based on a single parent-reported survey. Costs to the family include out-of-pocket expenses (insurance copayments, prescription and over-the-counter medications, specialized diets), lost labor productivity (time away from work for health care visits), and opportunity costs (restricted parent career choice, job change, job loss or dismissal).¹³ Using these figures, we estimate that a delay in OFC amounts to a mean total cost of \$12,203 per patient in our sample, most of which is borne by families (eg, costs not directly associated with medical visits, covered by insurance). The extrapolated costs of delayed challenge revealed a staggering figure of \$1,951,487 in this limited sample alone. More prompt use of OFC presumably would lead to decreased dietary restrictions, potentially lower food costs (eg, reduced need for allergen-free food), reduced number of

allergy visits with testing and medication costs (self-injectable epinephrine), and fewer missed work or school days.

Limitations of our study include its retrospective design and data obtained from medical record review alone. We had few failed challenges in the sample, which may suggest that there was potential selection bias to which patients OFC was offered (despite considerable delay) that favored OFC in those with low or absent skin or blood test sensitization and theoretically less risk. This study was performed at an academic medical center clinic and may involve clustering of patients who are higher risk for reactivity or are more complex (real vs perceived complexity) and potentially more likely to defer OFC. The 50% NPV metric was originally derived from a single center study at an academic referral center, and it is unclear whether this is an appropriate national standard for any practice or one that is best applied within similar academic populations without further study to validate its use. However, the 50% NPV remains the only metric proposed to address when foods can be safely introduced and is a reasonable starting point. Importantly, the specific reasons for delaying OFC were not investigated. It was difficult to determine the reasons for delay using retrospective medical record review or to ascertain whether the practitioner broached the subject of OFC with the family. Understanding the reasons for deferral was beyond the scope of the study. Elucidating the rationale for deferral is an important area for future work to more robustly understand the role of shared patient, family, and practitioner decision making with respect to this procedure.

Lastly, we used national cost estimates to determine the economic effect. We did not derive these costs for our population and institution, and therefore there could potentially be some variation from the national numbers. As well, given that our core argument is that many of these children may have been tolerant long before challenge, some of the direct costs attributable to inpatient care may not be applicable, and an alternative model would need to be created to discount such costs. However, it is difficult to estimate the degree to which this may potentially overestimate costs given that inpatient hospitalizations were a minor contributor to the total annual costs of food allergy as reported by Gupta et al.¹³ Despite these limitations, the study provides useful data that reveal OFC delay and enumerate costs associated with delay.

In conclusion, more than 50% of challenges in our food allergy center were delayed by nearly 3 years from the time that the patient's sIgE level became less than 2 kUA/L with a predicted 50% or greater success rate based on previously published data. The reason and specific rationale for delay were not explored because this was outside the scope of this study, but these factors are likely multifactorial and largely dependent on physician, caregiver, and/or

patient decision making. In-depth qualitative or mixed-method studies are recommended to better understand practitioner and parent motivations and stated preferences for the timing of offering and agreeing to an OFC. Delayed OFCs were not explained by positive SPT results within a year of challenge, history of severe reactions, or OFC outcome. A quality improvement program, which may include a recommended point where practitioners should be strongly considering and subsequently encouraging patients to undergo OFC, should be implemented to decrease time to OFC and reduce the economic burden of food allergy to both the family and the health care system.

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