Identifying thresholds of reaction for different foods

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ABSTRACT

Current food allergy management universally treats all patients with food allergy as being at risk for anaphylaxis (with the exception perhaps of pollen food allergy syndrome). Thus, patients are told to avoid the allergenic food in all potentially allergic forms and amounts. However, research over the past 2 decades has shown that many patients will tolerate small amounts of the allergen without any allergic reaction. Thus, if one were able to identify the threshold of reactivity, this could change management. At the population level, establishing levels at which the vast majority of patients (e.g., 95%) do not react could have public health ramifications, such as altering labeling laws. At the individual patient level, personal threshold levels could determine avoidance strategies, affect quality of life, and alter treatment decisions, e.g., oral immunotherapy starting doses. In this review, threshold data for various allergens and their potential effect on the management of the patient with food allergy are examined.

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Immunoglobulin E (IgE) mediated food allergy is thought to affect ~10% of both children and adults in the United States, with even more people avoiding foods due to self-reported food allergies.[1] Because there is currently no way to accurately predict which patients with IgE-mediated allergy are at high risk for anaphylaxis, current guidelines for the management of food allergy suggest that people with a documented food allergy avoid the offending food.[2,3] Even with immunotherapy options, *e.g.*, oral immunotherapy (OIT), which can increase the threshold of reactivity and have been incorporated into newer guidelines,[2] most patients will still need to avoid the allergen (although some groups do allow for free eating on OIT[4]). This avoidance leads to various burdens on patients and families, including loss of quality of life (QoL) and increased cost.[5,6] One reason for the loss of QoL is that patients and caregivers have to make decisions on whether to avoid foods that may contain even trace amounts of the allergen, such as in packaged goods. However, emerging data from the study of reaction thresholds could provide an evidenced-based method to change public policy, individualize therapy, and possibly improve the QoL for patients with food allergy and their families.[7]

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WHAT ARE THRESHOLDS?

The threshold of reactivity is the amount of allergen that a patient with an allergy can consume without an adverse reaction (above which would lead to a reaction). In a perfect world, every patient with an allergy would be challenged to his or her allergenic food by using a set protocol, starting with an amount to which no patient would ever react. This would allow for determination of a "no-observed adverse effect level" and a "lowest observed adverse effect level" for all allergens. In fact, an expert consensus protocol was established in 2004 to do this in a assigned number of patients with food allergy to model these values[8] with more refinement by a similar group in 2014.[9] Since that time, various studies have reported on threshold values for allergenic foods, and attempts to combine data from various challenge-based studies has been done. The first iteration of the combined data sets was reported in conjunction with the Voluntary Incidental Trace Allergen Labeling program of The Allergen Bureau of Australia & New Zealand.[10,11] This dataset has since been refined and updated in 2020.[12,13]

USE OF THRESHOLDS FOR PUBLIC POLICY

Establishment of threshold values for individual foods could theoretically allow for public policy management.[14] The current public policy in the United States for precautionary allergen labeling is not standardized in

any form, which creates a large gray area for patients and families. One suggested approach would be to identify the amount of allergen that would lead to a reaction in X% of the food-allergic population for the given food, known as the eliciting dose (EDx). For example, the ED_{10} for peanut would be the amount of peanut allergen to which 10% of patients with peanut allergy would react. By establishing these values, the goal would be to create precautionary labeling for packaged foods that is based on potential doses of exposure, knowing which exposures would lead to reactions in which percentage of patients.[11] A list of reported ED_{05} and ED_{10} are listed in Table 1.

Although establishing these thresholds has laid the groundwork for policy change to food labeling, there remain many uncertainties in using approaches like this at a population level[14] and, to date, even with improved labeling and knowledge of population-level dose thresholds, there will never be zero risk in everyday life situations.[13] Thus, it remains unclear if these data will lead to acceptable policy changes for the population.

INDIVIDUAL-LEVEL THRESHOLDS

Despite the difficulties in population-level risk mitigation, determining an individual patient threshold level may provide tangible benefits to individual patients. If, for example, a clinician were to know a patient's eliciting dose, then this could potentially alter a patient's or caregiver's QoL and a clinician's treatment strategy, and possibly affect treatment decisions.

Effect on QoL

Food allergies have detrimental effects to the QoL of both patients and their caregivers.[1,5,6,15] Although therapies such as OIT may be able to improve QoL,[16–18] other, less invasive, strategies such as proximity challenges have also been shown to have a similar effect.[19–21] Proximity challenges involve bringing the allergen in proximity to the patient (*e.g.*, bringing an open jar of peanut butter to the examination room of a patient with peanut allergy) and have been shown to be safe in an addition to their effect on QoL. In fact, even when the allergen is applied to intact skin of patients who are highly sensitive (such as applying peanut butter to intact skin), the only reaction that occurs is cutaneous, with no reports of anaphylaxis.[20,21] The ability for these less-invasive strategies to improve QoL may provide for an easier and safer way to treat patients with food allergy (by treating the QoL without the potential for adverse effects). Interestingly, knowledge of one's threshold of reactivity may also provide a similar benefit on QoL as OIT. In fact, one multicenter study showed that simply challenging children with peanut allergy to single 1.5-mg peanut protein challenge (ED_{05}) improved both parental and children self-reported QoL measures 1 month after challenge compared with the baseline.[22] Interestingly, this improvement occurred regardless of whether the children reacted during challenge. Although this effect on QoL had been shown from graded oral challenges,[23] this low-dose, one-time challenge offers a different approach to achieving this improvement. It is not fully known how a single, one-time, low-dose challenge could improve QoL. Perhaps knowledge of a threshold above a certain amount allows for more empowerment and confidence in everyday life and real-world settings.

Interestingly, in a single-center survey, 70% of the parents of children with peanut allergy expressed interest in a one-time single-dose challenge to 10 mg of peanut, understanding that this is the approximate ED_{10} and, therefore, their child would have an ~10% chance of reacting to the challenge.[24] Thus, it does seem that knowledge of tolerance to a low dose of allergen can be helpful to patients and parents.

Effect on Therapeutic Choices

In addition to the possible effect on QoL, knowledge of the threshold of reactivity could also directly affect treatment decisions for patients with food allergy.[7] If one were to know a patient's threshold, then this could help determine if, how, and when OIT could be implemented in a number of ways.

Table 1 **Reported ED_{05} and ED_{10} modeled from pooled challenge data***

Food	Discrete ED_{05}, mg	Cumulative ED_{05}, mg	Discrete ED_{10}, mg	Cumulative ED_{10}, mg
Peanut	2.1	3.9	7.1	9.0
Egg	2.3	2.4	6.3	7.4
Milk	2.4	3.1	7.1	9.6
Cashew	0.8	1.6	3.4	6.2
Shrimp	280	429	723	1265
Sesame	2.7	4.2	10.3	16.1

ED_{05} = Eliciting dose to which 5% of patients would react; ED_{10} = eliciting dose to which 10% of patients would react.
**Adapted from Ref. 12.*

First, OIT may be more appropriate for patients who react to a very low dose of allergen. These patients are likely to be the ones who would react to accidental ingestion and thus the ones who may benefit most from raising that threshold of reactivity. This same idea holds true for other therapies, *e.g.,* omalizumab, which was recently approved by the U.S. Food and Drug Administration for the treatment of food allergy based on the results of a large phase III study.[25] Patients were only included in the phase III study if they had a low threshold of reactivity (*i.e.,* reactive to the highest dose, of 100 mg of peanut protein = 144 mg cumulative protein). Thus, there are no data on its use in patients with a high threshold of reactivity. In addition, given the cost of omalizumab, it is debatable if its use in patients who already tolerate a high dose would be cost-effective.

Second, if a patient has a high threshold of reactivity, then he or she may not wish to pursue therapy with either OIT or omalizumab. For example, if a patient with peanut allergy were to know that he or she tolerated 200 mg of peanut protein at baseline, then the idea of undergoing an OIT regimen to a maintenance dose of 300 mg or to start omalizumab may not seem as helpful as it would to a patients who are low-dose reactive. In addition, this patient may not need to avoid foods with precautionary allergen labeling or have as much anxiety going out to restaurants or other social situations.[26] Interestingly, half of patients with peanut allergy likely tolerate 200 mg at baseline, a fact that could impact a large number of patients if identified.[26]

Third, if the patient with high-dose tolerance still wants to undergo OIT, then the OIT regimen could be tailored for him or her. For example, the patient would not need to undergo the majority of the up-dosing steps for a typical OIT protocol (Fig. 1). In addition, the up-dosing may be able to be done in a less strict protocol, such as home up-dosing and starting at a higher dose.[27,28]

Finally, in infants, a single low-dose challenge of milk may help to accelerate tolerance of baked milk, likely due to simply giving parents confidence to progress along a milk ladder.[29]

DIFFICULTIES WITH THRESHOLDS

Although these concepts and data suggest that establishing thresholds of reactivity in patients with food allergy may have several benefits, there are some difficulties in establishing and using these in patients.

Diagnostic Tests to Establish Threshold of Reactivity

There are various reports of the utility of diagnostic tests to predict the threshold of reactivity, but, currently, it does not seem that any are accurate enough to allow for certainty in determining threshold of reactivity without challenge. Serum IgE level, skin-prick test, and basophil activation testing (BAT) have been studied as a way to predict the threshold of reactivity.[30–34] Although BAT generally performs best at predicting the threshold of reactivity among these, none are clearly superior and none have shown enough accuracy to confidently tell a patient his or her threshold of reactivity without challenge. For example, in a recent analysis of biomarkers predicting threshold of reactivity to baked egg, although BAT (using CD203c but not CD63) was statistically different between low- and high-threshold reactors, it had an area under the receiver operating characteristic curve of 0.769 and, at its optimal cutoff, had a negative predictive value of 71%.[30] Thus, although able to statistically discern low- from high-threshold reactors, it is arguably not accurate enough to give families confidence in the real world.

Epitope mapping has also been studied to identify the threshold of reactivity, at least in patients with peanut allergy.[35] This method was able to stratify patients with peanut allergy into low-, moderate-, and high-tolerant groups with some accuracy.[35] However, there is still some uncertainty, *e.g.,* 88% of the subjects in the high-tolerant group could tolerate a 144-mg cumulative dose of peanut but 29% in the low-tolerant group could as well.[35] Thus, in a real-world setting, like with BAT, one would arguably still need to challenge patients to truly prove the threshold of reactivity.

Reassuringly, results of studies suggest that low-dose challenges are safe. For example, in the single low-dose peanut challenge discussed above, among

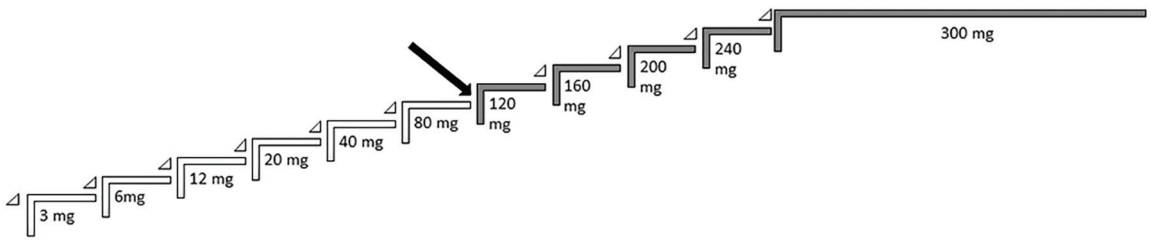

Figure 1. *Sample peanut oral immunotherapy up-dosing regimen. The full dosing regimen is a typical up-dosing regimen, starting with a low dose, such as 3 mg. However, ~50% of patients with peanut allergy are reported to tolerate > 120 mg of peanut protein. Thus, if this threshold is known, then many patients can start their dose later in the build-up, such as entering at the darkened arrow.*

the 378 children with peanut allergy who were challenged to the reported ED_{05} (1.5 mg of peanut protein), only 8 (2.1%) met objective criteria for a reaction and all reactions were mild, with 4 of the 8 receiving oral antihistamines only and none receiving epinephrine.[22] Similarly, in a meta-analysis of milk challenges, anaphylaxis is rare when challenging up to the ED_{05}, with 24 anaphylaxis events per 10,000 patients exposed to the ED_{05} dose.[36]

Reproducibility of Thresholds

If using threshold of reactivity to inform patient decisions, the clinician and the patient and/or caregiver need to have confidence that the threshold at challenge is static and will not change from time to time. Data from double-blind challenges do provide some reassurance that thresholds are stable from one challenge to the next. In the meta-analysis of milk challenges, the patients who received placebo in interventional studies of milk immunotherapy had two challenges within 12 months of each other.[36] Among these patients, 80% reacted at repeated challenge to within a 0.5-log difference compared with initial challenge.[36] Similar results were found in a meta-analysis of peanut challenges, with 71% of the participants reacting on repeated challenge within a 0.5-log difference compared with initial challenge.[37] Whereas this is reassuring, it arguably allows for too much variance to confidently inform patients how to manage their or their child's food allergy.

The other concern with regard to the reproducibility is that the thresholds may change in the real world with exposure to cofactors of an allergic reaction (that would not be present in challenges in a controlled research setting).[38] It is well established that cofactors, such as exercise, viral illness, concomitant medications, can affect the presence or severity of anaphylaxis.[39] This same phenomenon holds true for the food allergy threshold of reactivity. This has been proven eloquently for sleep deprivation and exercise, in which both decreased the threshold of reactivity in a food challenge setting by 45% in patients with peanut allergy.[40] It has also been shown to occur in the real-world setting in OIT, in which patients tolerate a single dose regularly and then react to that dose in the setting of a cofactor, such as viral illness, exercise, or menses.[41]

Thus, if you can establish a patient's threshold of reactivity in a clinical setting, if you are going to use that information to guide patient care, then one must be aware of these issues.

CONCLUSION

Knowledge of a patient's threshold of reactivity has the potential to guide care for a patient with food allergy. This could include liberating restraints of avoidance of packaged goods with precautionary allergen labeling, allowing a patient to eat small amounts of the allergen, or altering OIT or treatment regimens based on threshold. In fact, in a small survey of allergists, the majority of respondents (81%) who reported altering care of their patient and not just recommending strict avoidance if they knew the patient was a "high-threshold reactor."[42] Thus, we may be getting to a time in food-allergy management in which treatment decisions are made based on a threshold of reactivity phenotype. Unfortunately, however, there are some hurdles to the use of threshold in every day practice, including the lack of accurate diagnostic tests to predict this phenotype and the labile nature of thresholds in the setting of cofactors.

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