



Editorials

Is the better part of valor truly discretion?



Peanut allergy affects 1.4% to 4.5% of children, depending on the study and methodology. Self-reported estimates have shown an alarming 3-fold increase in US populations over 10 years, whereas UK data from a longitudinal birth cohort with challenge-based evidence have not reflected such an alarming increase.^{1–4} Unfortunately, for years, the common peanut allergy management paradigm was to strictly avoid any potential exposure (including trace amounts) and carry self-injectable epinephrine. Now, we find the field on the cusp of what could be 2 therapies approved by the US Food and Drug Administration (FDA) for the treatment of peanut allergy in children in late 2018 or early 2019 (a commercial low-dose oral immunotherapy [OIT] capsule and an epicutaneous patch).⁵ Treatment might not be the right option for all children with food allergy, but for some this could be the option they have been waiting for since diagnosis.

The Perspective piece by Shreffler et al⁶ raises several provocative issues about potential goals of therapy and approaches to lowering risk. By this time in our study of food allergy, one would literally have to have been a castaway on a desert island for the past 20 years to not be aware and intimately of the risks, dangers, and adverse outcomes attributable to peanut allergy. This is what makes this particular allergen such an enticing target of therapy and helped to designate the 2 therapies as “fast-tracked” products by the FDA.⁵ The need for a peanut allergy treatment is enormous, and the potential for this to be realized has tantalized the field since the publication of phase II results related to TNX-901 in 2003 (which never came to further fruition).⁷ The field has since been impatiently waiting for a future treatment and making due with strict avoidance in the meanwhile. These investigators accurately discuss the difficulties with the current management cornerstones and the problems that can stem from a hollow solution of strict avoidance.

Our current model for managing peanut allergy is broken, for sure, and this fracture is hallmarked by the rapid increase in poor quality of life and poor empowerment of our patients and

caregivers—factors that can be best described as iatrogenic consequences of overly conservative management. In our quest to provide a no-risk environment, perhaps we have overshot the mark and overlooked the value of understanding reaction thresholds. Of course, 0 risk is not compatible with human existence, yet this seems to be a consistent message we hear from certain segments of the food allergy community. The well-intended advice of strict avoidance mixed with tone-deaf and non-evidence-based advice making unsubstantiated claims that “trace amounts kill” might have irreversibly tipped the balance from adaptive vigilance to maladaptive extreme alertness and potentially unnecessary exclusion of products with precautionary labeling (and a failure to accept thought leader-initiated research that shows such risk is quite minimal and not likely to contain a sufficient quantity of peanut to provoke a reaction).⁸ Risk of fatality is often overblown in the face of data that suggest food allergy fatality is exceedingly low (although not absent, but then neither is death from lightning strikes), but also generally the result of a compounded risk such as delay or inappropriate treatment and not just the ingestion itself.⁹ Honestly, what choice have we given these families except to cower in fear and be anxious? The messaging has been all wrong, and we share blame in enabling this. Although admittedly no threshold level is likely entirely static and stable, the concept of a threshold is an important benchmark in understanding the human immune response to allergen and aids in setting the boundaries of what might be justifiable vs irresponsible risk. At least 3 studies have shown that thresholds to peanuts do exist, which should have refuted the argument regarding trace exposures, but oddly common sense has not prevailed here, and some advocacy groups have chosen to shun this evidence in their messaging.^{8,10–12} Sadly, we’ve done little as a field to fix the problem and minimize this source of fear.

As Shreffler et al discuss, the concept of establishing a threshold is necessary and nested within demonstrating successful treatment, because pre-to-post eliciting cumulative dose thresholds are pivotal trial outcomes for OIT and epicutaneous patch phase III trials. However, there is a larger clinical horizon to consider, because it is unlikely that any forthcoming clinical practice guidelines for initiation of OIT or the epicutaneous patch will require an entry or interim challenge to monitor therapy. Therapeutic response across the broader population that would be considered for treatment will have to be presumed to follow a similar distribution to whatever the phase III data might show in threshold change. While we await data as to how threshold, and threshold change, might influence treatment-related outcomes, we do have some practical sense of what the clinical meaningfulness of a peanut-specific threshold could represent. Recently, Baumert et al¹³ published a quantitative risk assessment model, also noted in this Perspective piece. Through modeling, common exposure patterns to certain snack goods at a population level are matched to known

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trace contamination levels to provide an assessment of whether a certain attained threshold would infer protection against exposure to a particular product (informed by actual consumption patterns). These data show a significant lower inferred risk when attaining a threshold of 300 mg of peanut protein and an even further lower risk for those who can achieve a threshold that equals the primary end point of the 2 phase III trials (>1,000 mg cumulative). As is noted in the piece, simply establishing this threshold does not absolve the still allergic but desensitized patient of any responsibility of avoiding known peanut-containing products. These treatments under evaluation aim only to infer some level of desensitization exceeding an anticipated unintended exposure and do not offer carte-blanc protection. However, prior OIT research from a large UK trial showed that caregivers only want some buffer against an unintended exposure, which suggests that the 2 therapies are well aligned with caregiver goals, which is further buoyed by the potential of quantitative risk assessment modeling.¹⁴

Shreffler et al are careful to point out that establishing a threshold is not a guarantee, because this can shift based on cofactors such as infection, inflammation, activity, and allergic comorbidity. The level is intended to represent a relative target, not a money-back guarantee. We all wish it were that simple, honestly. The question now facing the field, stakeholders, and caregivers is how we move forward with these new tools. Is it accurate and ethical to continue to preach highly conservative management that emphasizes “no risk” in the face of data that might suggest this is not feasible or necessary and might actually lower quality of life?¹⁰ Should there be accountability for the consequences of such strategies being preferentially advised by our advocacy partners? Should there be equipoise to liberating some calculated risk taking, pending additional replication? This is all unclear. It is unclear how many families will opt for one of these new treatments, assuming either gains approval, and whether these therapies can deliver real-life results that replicate whatever outcomes enabled FDA approval. However, the potential is there to break the mold and move away from the dogma that strict avoidance of precautionary labeling or known minimal trace contamination is still best for all. The horizon is bright for future therapies and additional risk modeling, which can better arm our decision making and means to inform our patients about how to personalize management of their food allergy going forward. There are other options that are still safe but less conservative, and this could greatly benefit some families. Treatments can play an important role in furthering such agendas.

However, our work is not done, because many questions remain with the use of these new therapies. What is the surrogate of efficacy in the real world, because most real-world allergists are not going to perform challenges to determine threshold? Could quantitative risk assessment serve as a model for testing real-world efficacy through use of some of those products as “at-home” tests of efficacy? If such tests are successfully navigated, will this lead to bolder steps in more significant risks being desired by parents, including testing higher possible levels of product exposure or less regular dosing of whichever product is being used? We need to determine how long such therapy should be continued—is this lifelong, as was the case for honeybee venom immunotherapy? Or will we

find that the effect lingers after discontinuing just a few years of therapy? Can we attain the holy grail of cure or will a buffer against accidental protection be necessary and sufficient? Only time will tell, but what an exciting time to be in the field when we can finally start addressing issues viewed as pipe dreams just a few years ago.

Matthew Greenhawt, MD, MBA, MSc^{*,†}

John J. Oppenheimer, MD^{‡,§}

^{*}Food Challenge and Research Unit
Children's Hospital of Colorado
Aurora, Colorado

[†]Section of Allergy and Immunology
University of Colorado School of Medicine
Aurora, Colorado

[‡]Department of Internal Medicine
New Jersey Medical School
Newark, New Jersey

[§]Pulmonary and Allergy Associates
Morristown, New Jersey
nalopp22@gmail.com

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