

Benefits of understanding allergen thresholds

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Key words: Food allergen, threshold, risk, challenge, dose

Recent studies published in the *Journal*^{1,2} have shed important light on the understanding of thresholds for patients with food allergy. In most clinical contexts, a threshold can be viewed as “the level that must be reached for an effect to be produced.”³ Because the effect in question for a subject with food allergy might be a potentially life-threatening reaction for which no preventative treatments are available, understanding threshold responses to allergen exposure undoubtedly benefits the management of patients. Thresholds have diagnostic importance as measures of allergen desensitization or therapeutic effect to immunotherapy and for identifying suitable candidates for therapy. Importantly, knowledge of thresholds might improve quality of life for patients by helping them understand their potential risk for reactions to everyday allergen exposures and helping them to make informed choices in their food avoidance practices.^{4,5} To date, however, deciphering what an allergen threshold clearly represents for individual patients has remained elusive. There are no simple diagnostic tests other than challenge to predict thresholds, and evidence shows that individual thresholds can be affected by various factors, such as exercise and infections,^{6,7} and might not be reproducible from one challenge to the next.⁸

Risk assessment approaches are being proposed to estimate thresholds for populations of allergic patients.^{1,6,9} For some allergens (ie, peanut, egg, milk, and hazelnut), there are now more than 200 individual data points on eliciting doses (EDs) from double-blind, placebo-controlled food challenge studies using low-dose allergen protocols (of a few milligrams of protein or lower) from which to make population threshold risk predictions. Determining thresholds to lie within the interval between the ED and the highest challenge dose not to elicit a reaction, Allen et al¹ modeled threshold dose distribution data from various population data sets to estimate reference doses, which are derived from the ED of allergen predicted to elicit a reaction in 1% (ED₀₁) or 5% (ED₀₅) of the population, for most major food allergens. Although the main focus of this analysis was to establish thresholds for precautionary allergen-labeling purposes, these data can also provide prognostic reaction-risk information for patients. For example, these data demonstrate

that the majority of allergic patients might not be sensitive to minute allergen exposures, with more than 70% of patients not expected to react to 60 mg of peanut protein (a dose equivalent to 1 whole peanut). Communicating this risk has value in patient education and addressing consumer fears about trivial allergen exposures.^{10,11}

Despite progress in estimating population thresholds, limitations in analyzed ED data that could affect final threshold determinations need to be highlighted. Because threshold data derive from studies from geographic areas with varying sensitization patterns, subject recruitment requirements, dosing protocols, and criteria for establishing EDs, overrepresentation or underrepresentation of certain qualitative factors in the data set could skew threshold estimations in one direction or another. For example, Allen et al¹ found significant ED distribution variability when population age, geographic origin, starting dose, and challenge material type were analyzed separately. The authors also acknowledged that thresholds based on ED data from controlled studies might not capture the effect of other factors (eg, exercise and medications) on thresholds in the community.

In this issue of the *Journal*, Blumchen et al² raise additional questions about the accuracy of current population threshold estimations by presenting threshold data in German children with peanut allergy using a modified challenge protocol with a prolonged interval of 2 hours between incremental doses. The authors argue that this longer dosing interval mimics more discrete real-life encounters with single allergen exposures and captures late ED responses that might be missed in studies using shorter dose intervals of 15 to 30 minutes. Indeed, the authors found that more than 70% of subjects had objective EDs occurring 30 minutes or more (median, 50 minutes) after challenge. Because Allen et al¹ based thresholds on EDs derived from studies with shorter time intervals, it is possible that true ED responses occurred at doses 2- or 3-fold lower than those reported; thus actual thresholds would be lower than those reported. Although no differences were found comparing peanut ED₀₅ data from Blumchen et al² with ED₀₅ data from studies using shorter dose intervals,⁹ this does not exclude the possibility for ED differences caused by an interval-length effect. ED₀₅ differences between the 2 data sets might have been overshadowed by differing ED sensitivities at the population level. Moreover, interval differences might not be prominent at low EDs, at which dose increments are relatively smaller. In any case these data reveal a need to re-examine population threshold data based on studies with shorter or longer dose-interval length to determine how this factor affects final threshold distributions.

It is also notable that Blumchen et al² challenged a patient population with asthma and prior anaphylaxis who are arguably at heightened risk for severe reactions to dose challenge.^{12,13} Although demonstrating that low-dose challenges can be safely performed in populations at high risk for severe reactions, the authors found that patients with prior anaphylaxis had

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest. The findings and conclusions in this editorial are those of the authors and do not necessarily represent the views of the Food and Drug Administration.

Received for publication May 5, 2014; accepted for publication May 7, 2014.

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J Allergy Clin Immunol 2014;■■■:■■■-■■■.

0091-6749

<http://dx.doi.org/10.1016/j.jaci.2014.05.007>

significantly lower thresholds. This finding supports¹⁴ and refutes^{9,15} prior observations and renews debate over whether study populations that exclude patients with prior anaphylaxis from challenge represent the most sensitive patients in the population. Because most data analyzed by Allen et al¹ came from study populations that excluded these subjects, there is concern that resultant thresholds might not represent patients at highest risk for severe consequences from dose challenge. Inclusion of more ED data from such patients would benefit the risk characterization of population threshold data.

Understanding the relative severity of responses in relation to threshold doses is another issue not clearly addressed by population threshold data. This understanding would help alleviate stakeholder fears (ie, Does ED₀₁ predict that reactions in sensitive subjects will all be severe?), as well as address other public health threshold questions.¹⁰ For example, the US Food Allergen Labeling and Consumer Protection Act established a safety standard of “does not cause an allergic response that poses a risk to human health” for granting labeling exemptions. This implies some need to address reaction severity.¹¹ Although the expert panel in Allen et al¹ contends that low dose thresholds are expected to be associated with milder reactions, this remains unproved. Few studies that examined this question found no significant correlation between lower EDs and lower reaction severity.^{14,16} Likewise, although Blumchen et al² found that lower EDs correlated with biological markers of sensitization (eg, higher IgE levels, skin prick test responses, and basophil activity), a promising finding that supports recent observations regarding high IgE levels and lower EDs¹⁵ and merits further study, the authors found no correlation between ED and response severity. More research is needed to understand the relationship between low-dose allergen exposures and severity.

The results of Blumchen et al² provide important insights. However, some limitations should be considered. Although the authors focused on objective reactions and controlled for various confounders, the study was an open challenge and is inherently subject to false-positive results. The length of time between challenges likely increased opportunities for nonspecific allergic-type responses to manifest; thus observations of delayed ED responses should be further validated by using double-blind, placebo-controlled food challenges. Moreover, the authors' proposed protocol might not be feasible for establishing thresholds in clinical practice because the requirement to hospitalize patients over a minimum of a few days would be impractical in most health care settings. Nonetheless, it is hoped that the results of Blumchen et al² and Allen et al¹ will further expand

research and encourage more diagnostic food challenges to help patients understand where their threshold lies on a reaction-risk continuum. This information has potential to significantly improve clinical management and quality of life of patients.

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