

Harmonization of Terminology for Tolerated and Reactive Dose in Food Allergy Immunotherapy



Thomas B. Casale, MD^a, Tmirah Haselkorn, PhD^b, Christina E. Ciaccio, MD^c, Panida Sriaroon, MD^a, and Bradley E. Chipps, MD^d Tampa, Fla; Los Altos, Calif; Chicago, Ill; and Sacramento, Calif

Currently, there is no Food and Drug Administration–approved therapy for food allergy. Several new potential treatments are under investigation, including food allergen immunotherapy via various routes of administration, such as oral immunotherapy, epicutaneous immunotherapy, subcutaneous immunotherapy, and sublingual immunotherapy. The double-blind, placebo-controlled food challenge (DBPCFC) has traditionally been used for diagnostic purposes, but extrapolation of the specific terminology used in food allergy diagnosis to interpretation of efficacy in clinical trials is incongruent and difficult to apply. There is a need for standardization of the terminology used in food allergy clinical trials, because inconsistencies can lead to potential misinterpretation of end points. The *reactive dose*, previously referred to as the eliciting dose, is defined as the dose given that induces the onset of unequivocal allergic symptoms, or the dose that stops the challenge based on physician discretion. Conversely, the *single highest tolerated dose* is defined as the highest dose given during a food challenge that elicits either no symptoms or symptoms that do not meet stopping criteria per the study protocol. The evolving field of food allergy provides a novel opportunity to define those end points that are most meaningful for patients, which is fundamental for successful implementation, education, and safety. © 2018 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2019;7:389-92)

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Clinical studies of immunotherapy for food allergies, a century-old concept based on gradual exposure to allergens to achieve desensitization, and potentially long-term tolerance, have demonstrated significant therapeutic benefits.^{1,2} Several randomized, placebo-controlled phase 2 studies of oral immunotherapy (OIT) for peanut allergy with various products have reported successful induction of desensitization with acceptable safety and tolerability^{3,4} and were allowed by the Food and Drug Administration (FDA) to progress to phase 3 programs.²⁻⁶ Data from a recent phase 3 clinical trial suggest that OIT may be a safe and effective treatment for children and adolescents with peanut allergy.⁷ Epicutaneous immunotherapy for peanut allergy has also shown encouraging results both in phase 2 studies^{8,9} and in a phase 3 study.^{10,11} These data have not yet been made public in a peer-reviewed journal. Both forms of immunotherapy are under consideration for approval by regulatory agencies including the FDA. Because peanut immunotherapy has been the most rigorously studied, this article will focus on this treatment.

The PRACTALL guidelines define the double-blind, placebo-controlled food challenge (DBPCFC) as the criterion standard when performing an oral food challenge (OFC) and the benchmark against which other diagnostic procedures are compared.^{12,13} The OFC is currently used both for the diagnosis of food allergy and as an assessment for determining efficacy in clinical trials after OIT. Because the DBPCFC was historically implemented only for diagnostic purposes, this resulted in the use of specific terminology. When used as a clinical trial end point, interpretation of results using this terminology may be different. Because food challenges are the criterion standard to assess efficacy in food allergy immunotherapy trials, it is important to recognize that the variability in terms used by the FDA in regard to end points may lead to confusion.

Multiple researchers have formally cited the need for standardization in various aspects of the practice and terminology of food allergy management.¹³⁻¹⁵ There are significant gaps leading to potential misinterpretation of clinical end points, which could impact patients, caregivers, physicians, payers, and advocates. Indeed, results of a recent US-based survey of 101 allergists/immunologists indicate variability in the terminology used in interpreting OFC results, as well as inconsistent understanding of the definitions of these terms.¹⁶ As potential new standards of care for food allergy evolve, a better understanding and harmonization of the terminology used for

^aDivision of Allergy and Immunology, University of South Florida, Tampa, Fla

^bEpiMetrix, Inc, Los Altos, Calif

^cSection of Allergy/Immunology, The University of Chicago, Chicago, Ill

^dCapital Allergy & Respiratory Disease Center, Sacramento, Calif

Conflicts of interest: T. B. Casale is an investigator for Aimmune Therapeutics and serves on the Scientific Advisory Board. T. Haselkorn has received consulting fees from Genentech, Inc, Novartis Pharmaceuticals Corp., and Aimmune Therapeutics. C. E. Ciaccio has received consulting/advisory board fees from Aimmune Therapeutics. P. Sriaroon has received speakers bureau fees from Genentech, Inc. B. E. Chipps has received consulting and speakers bureau fees from AstraZeneca, Boehringer Ingelheim, Circassia, Genentech, Novartis, and Teva, and consulting fees from Regeneron and Sanofi.

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Corresponding author: Thomas B. Casale, MD, Division of Allergy and Immunology, University of South Florida, Tampa, FL 33612. E-mail: tbcasale@health.usf.edu.

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Abbreviations used

DBPCFC- double-blind, placebo-controlled food challenge

FDA- Food and Drug Administration

OFC- oral food challenge

OIT- oral immunotherapy

describing clinical trial end points, specifically, *tolerated dose* and *reactive dose*, will be important to successful implementation, patient understanding, education, and safety. These same end points need to be defined for clinical practice so that patients switching physicians and continuing either immunotherapy and/or avoidance instructions can have consistent therapeutic management goals.

TERMINOLOGY USED IN FOOD ALLERGY CLINICAL TRIALS

The *reactive dose*, or the “not-tolerated” dose during an OFC in a food allergy clinical trial, is defined as the dose given that induces the onset of unequivocal allergic symptoms, or the dose that stops the challenge based on physician discretion (Figure 1, A). The symptoms are typically objective and can range from mild to severe. The reactive dose has previously been referred to as the “*eliciting dose*.” Conversely, the *single highest tolerated dose* is defined as the highest dose given during a food challenge that elicits either no symptoms or symptoms that do not meet stopping criteria per the study protocol (Figure 1, B). These symptoms are usually mild, transient, and subjective, such as pruritus, nausea, or abdominal discomfort.

To illustrate the calculation of the doses described in OFCs, the following is an example of a patient being evaluated in a food immunotherapy trial. In the OFC to assess efficacy of therapy, the patient ingested the following peanut doses without dose-limiting symptoms: 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, and 600 mg peanut protein. However, the patient had dose-limiting symptoms at 1000 mg peanut protein. In this case, 600 mg is the *single highest tolerated dose* (Figure 1, B), or the last dose before the reactive dose. The *cumulative tolerated dose* is the sum of the tolerated doses, *not including* the reactive dose (Figure 1, C). For this patient, the cumulative tolerated dose would be 1044 mg ($1 + 3 + 10 + 30 + 100 + 300 + 600$ mg). The *cumulative reactive dose* is the sum of doses consumed, *including* the reactive (not-tolerated) dose (Figure 1, D). Thus, because the patient reacted at 1000 mg, the cumulative reactive dose would be 2044 mg ($1 + 3 + 10 + 30 + 100 + 300 + 600 + 1000$ mg).

The concept of reactive dose may also be applied to patient populations with a particular food allergy.¹⁷ When applied to a population threshold, it is often referred to as the “*eliciting dose*.”¹⁷ For example, eliciting dose₁₀ is the dose predicted to provoke a reaction in 10% of individuals with a specific food allergy. This terminology is useful for comparing the potency of one allergenic food versus another, and in predicting how

many individuals would develop a reaction to a specific exposure, for example, a food contaminated with an undeclared allergen.

COMMUNICATION OF FOOD CHALLENGE RESULTS

Proper communication of the results from a food allergy clinical trial is equally important as understanding the terminology. A recent online survey, which was sponsored by Aimmune Therapeutics (Brisbane, Calif), assessed physician attitudes and preferences regarding terminology in OIT in more than 100 allergists/immunologists from 28 cities across the United States.¹⁶ After OIT, 81% felt that the tolerated dose was the most clinically meaningful for patients to know. Indeed, patients typically appreciate knowing the dose they can tolerate, as opposed to the dose they cannot tolerate (the reactive dose), as well as how to “translate” the milligrams of protein doses into actual food doses. For example, 300 mg peanut protein = 1 peanut and 600 mg peanut protein = 2 peanuts. Similarly, when reporting the cumulative reactive dose versus the cumulative tolerated dose, misconceptions in interpretation can occur. It may be unwise to suggest that a patient with a cumulative tolerated dose of approximately 1 g of peanut protein during an OFC can tolerate 3 peanuts at once, because these challenges do not represent a true desensitization. As such, it would seem reasonable to use the single highest tolerated dose if one were counseling the patient. As another example, at the exit food challenge in a clinical trial, the *reactive dose* in the active treatment arm was 1000 mg and the *cumulative reactive dose* was 2044 mg ($1 + 3 + 10 + 30 + 100 + 300 + 600 + 1000$ mg). Communicating these numbers (1000 mg or 2044 mg) to the patient could be confusing and potentially misleading, because the last food challenge dose, or the *single highest tolerated dose* (the dose that the patient actually tolerated without dose-limiting symptoms), was 600 mg in this example. This is important clinically considering a potential risk for the patient feeling “falsely assured” of the level of protection gained from a potential treatment against accidental exposure to a food allergen. Another limitation of the term “cumulative dose” is that, in the real world, accidental exposure to an allergen and subsequent reaction can occur quickly after a single dose or exposure, not in incremental amounts over several hours.

SUMMARY

As new treatments for food allergy are emerging, there is a need to standardize the terminology used in food allergy clinical trials. As such, a food allergy lexicon is available on the American College of Allergy, Asthma and Immunology Learning Connection Web site.¹⁸ An understanding of the lexicon for evaluating outcomes, such as *reactive dose*, *single highest tolerated dose*, *cumulative tolerated dose*, and *cumulative reactive dose*, as clinical trial end points is critical. The evolving field of food allergy provides a novel opportunity to define those end points that are most meaningful for patients.

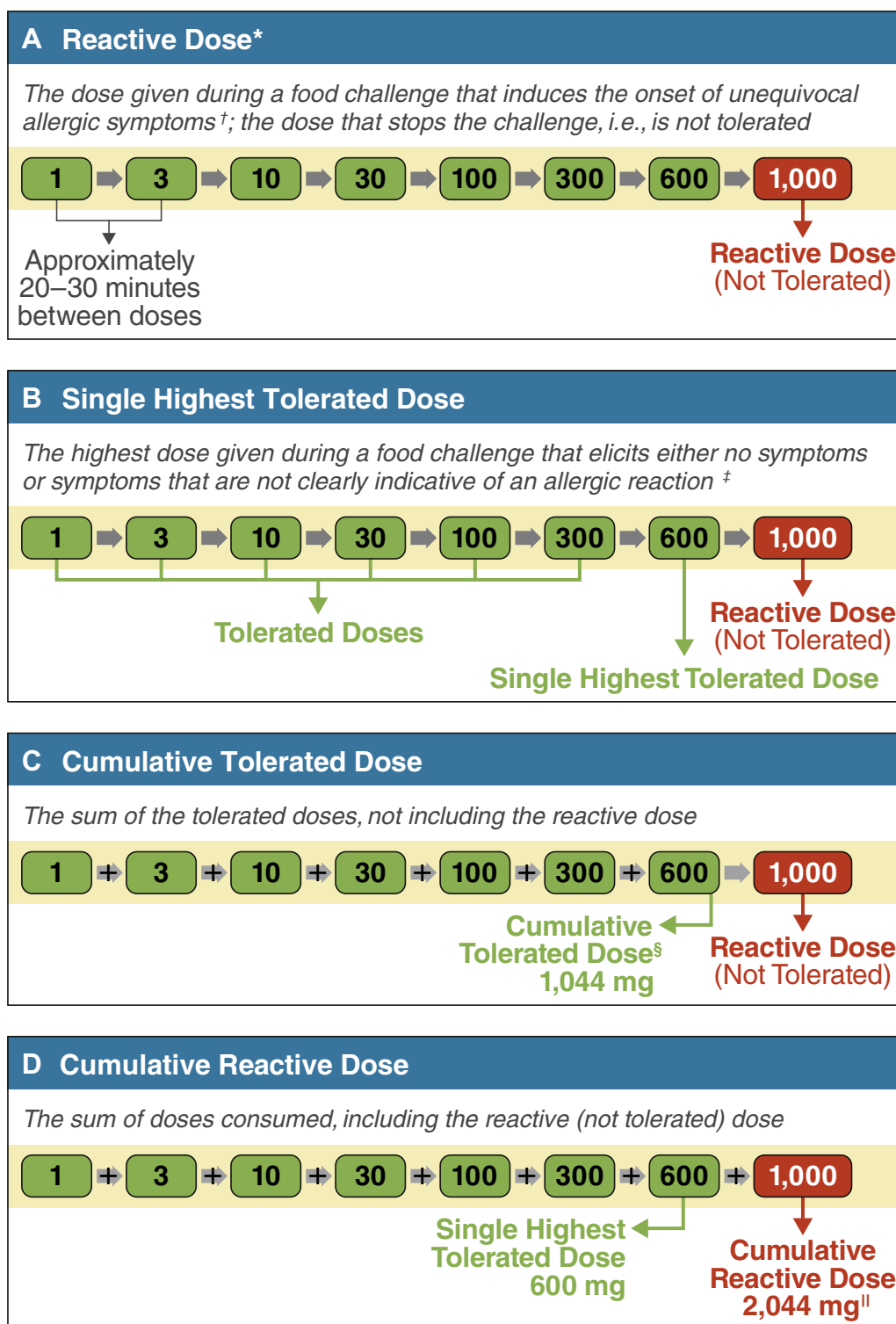


FIGURE 1. Terminology used in food allergy clinical trials using double-blind, placebo-controlled food challenge (~20–30 minutes between doses): **A**, Reactive dose. **B**, Single highest tolerated dose. **C**, Cumulative tolerated dose. **D**, Cumulative reactive dose. *Previously referred to as “eliciting dose.” †For the reactive (not-tolerated)/stopping dose, the symptoms are typically objective and can range from mild to severe. ‡For the tolerated dose, the symptoms should not be any worse than mild, are usually transient, and are typically subjective (examples include pruritus of the skin, nausea, throat/abdominal discomfort). §1 + 3 + 10 + 30 + 100 + 300 + 600 mg = 1044 mg. ||1 + 3 + 10 + 30 + 100 + 300 + 600 + 1000 mg = 2044 mg, which is the sum of all doses given including the last not-tolerated dose, that is, the reactive dose. This means that the actual tolerated dose is 600 mg, that is, the last dose before the reactive dose.

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