

# Practical peanut challenges for the clinician

Jay A. Lieberman, M.D.

## ABSTRACT

**Background:** There is an increasing incidence of peanut allergy in many Westernized countries. Unfortunately, current diagnostic tests that evaluate for sensitization can give false-positive results and may lead to overdiagnosis of peanut allergy. Due to this and to the fact that there are several therapies currently being investigated for the treatment of peanut allergy, it is imperative that practitioners who are caring for patients with food allergy be knowledgeable about and comfortable with performing oral challenges to peanut in nonresearch settings.

**Methods:** Literature review and author experience.

**Results:** This article focused on various aspects of a peanut challenge, including patient selection, contraindications, the location of the challenge, form of the peanut to be fed, the starting and goal doses for the challenge, and practical dosing schedules. It is meant to be a real-world overview for a practicing clinician.

**Conclusions:** Clinicians should be able to perform open peanut challenges in properly selected patients.

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Although the true prevalence numbers of food allergy are difficult to assess, peanut allergy is a common food allergy estimated to affect 1–2% of children in the United States, with an incidence that has been increasing.<sup>1,2</sup> Fortunately, it is hoped that early intervention strategies and novel therapies will provide means to help prevent and/or treat peanut allergy.<sup>3–5</sup> It, thus, is imperative that clinicians be able to accurately diagnose peanut allergy to appropriately decide who should be a candidate for early introduction or therapy (if available), and to rule out peanut allergy when appropriate. Although the skin-prick test (SPT) results and serum immunoglobulin E (IgE) values can be helpful in guiding this decision, oral food challenge (OFC) remains the criterion standard for diagnosis.<sup>6</sup> In fact, in the most recent addendum guidelines for the prevention of peanut allergy, peanut challenge is recommended in infants at high risk and who have intermediate SPT wheal size to peanut.<sup>7</sup> Thus, a practical understanding of how to perform peanut challenges is vital to any practicing allergist. This arti-

cle discussed the practical aspects of the open peanut challenge designed for the practicing clinician.

There are resources available to help guide clinicians and researchers on how to perform OFCs.<sup>8–10</sup> The OFC work group report<sup>8</sup> on food challenges is an apt resource for the practicing clinician with guidance on how to set up and perform challenges, whereas the PRACTALL consensus report<sup>9</sup> is more geared to research and describes the double-blind, placebo-controlled challenge in more depth. There also is a work group report on challenges to peanut specifically in infants<sup>10</sup> and a recent article that highlights pearls and pitfalls of infant challenges.<sup>11</sup> This article specifically examined peanut challenges by concentrating on the open (nonblinded) challenge for IgE-mediated allergy (not for delayed reactions, e.g., food protein-induced enterocolitis syndrome).

## HOW TO SELECT PATIENTS

The need to perform a peanut challenge will vary on the clinical scenario. For example, current recommendations suggest a peanut challenge (or possible supervised feeding) should be done in infants at high risk of peanut allergy if the SPT wheal size is 3–7 mm.<sup>7</sup> There are many other clinical scenarios in which a challenge would be warranted; examples are presented in Table 1. In the end, the clinician and the patient and/or caregiver must decide together on the risk-to-benefit ratio in each case. For example, the benefit of performing the challenge on a patient who wants to enter the armed services may be high enough to outweigh the risk, even if the likelihood of reaction is high. By using shared decision-making, the clinician and the patient and/or caregiver must also consider the impact of not doing a challenge or delaying a challenge. Analysis of data indicates an increase in health-care cost and bur-

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From the Division of Allergy and Immunology, Department of Pediatrics, The University of Tennessee Health Science Center, Memphis, Tennessee

J. A. Lieberman serves on the editorial board for *Annals of Allergy, Asthma, & Immunology*. He reports honoraria for serving on advisory board from Aimmune Therapeutics, DBV Technologies, and ALK Abello. He serves as principal investigator, and his institution receives money through grants for research from Aimmune Therapeutics, DBV Technologies, and Regeneron

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Address correspondence to Jay A. Lieberman, M.D., Division of Allergy and Immunology, Department of Pediatrics, The University of Tennessee Health Science Center, 51 North Dunlap, Suite 400, Memphis TN 38105

E-mail address: jlieber1@uthsc.edu

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Table 1 Possible scenarios and indications for performing peanut challenge

| Scenario                                      | Comment                                                                                                                                                                                                                                                                 |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Enrollment into a research study              | Most rigorous studies require double-blind challenge at baseline and at least once during therapy to show efficacy                                                                                                                                                      |
| Rule out peanut allergy in “Tolerant” patient | Examples<br>Patient ingests peanut regularly without symptoms but had a positive test result on panel immunoglobulin E testing for atopic dermatitis                                                                                                                    |
| “Low-risk” patient                            | Sibling of a patient with peanut allergy whose parents are worried about introducing peanut despite negative or equivocal testing                                                                                                                                       |
| “High-risk” patient                           | Patient with a history or testing that is convincing for peanut allergy but needs challenge to be able to enter armed services                                                                                                                                          |
| Early peanut introduction                     | To determine if an infant at high risk is already allergic to peanut before starting early introduction                                                                                                                                                                 |
| Before initiating therapy                     | If using oral immunotherapy outside of a research study, or if there are future U.S. Food and Drug Administration approved therapies, it would be reasonable in some cases to make sure that the patient is truly allergic before starting a prolonged therapy course   |
| To determine efficacy of therapy              | There may be a need in research studies and in clinical practice if immunotherapy is used to assess the efficacy of the therapy                                                                                                                                         |
| To establish threshold levels of reaction     | This is typically done in research settings; can be done for an individual ( <i>e.g.</i> , to determine an individual’s threshold of reaction) or on a population basis ( <i>e.g.</i> , determine the threshold at which 5% of patients with peanut allergy will react) |

den for delaying OFC, especially in lower-risk groups, and, thus, this should be considered in the decision process.<sup>12</sup>

One interesting scenario for peanut challenges in the future will come about if there are future U.S. Food and Drug Administration approved therapies for peanut allergy. In fact, peanut oral immunotherapy is currently being practiced by many practitioners in the United States.<sup>13</sup> Thus, although peanut challenges are not specifically required to initiate therapy, it is or will be reasonable to discuss the risks and benefits of performing a challenge before starting the therapy. A challenge may not be warranted in most cases; however, it may be reasonable to challenge unclear cases to make sure the patient is truly allergic, especially if the assumption is that the therapy will be lifelong. In this regard, use of a shared decision-making tool to help the patient and/or family understand that these concepts may be of benefit.

Testing for sensitization by using SPT, serum IgE to peanut, and component-resolved diagnostics should all help guide the clinician in deciding on whether to perform OFC to confirm the allergy. These tests, however, must always be taken into context and in conjunction with the clinical history. Results from each of these tests can help predict the likelihood of true clin-

ical allergy and reaction during OFC. Unfortunately, there are no perfect tests. Although a full review of the role of these diagnostic tests in food allergy is beyond the scope of this article, current guidelines and systematic reviews offer information on how to use these tests.<sup>6,14</sup>

Beyond the indication and clinical scenario that will dictate whether to perform peanut OFC, there are some contraindications to performing OFC, even in an otherwise appropriate scenario. Examples of these include cardiovascular disease, pregnancy, treatment with  $\beta$ -blockers, active eczema, active rhinitis, gastrointestinal symptoms (*e.g.*, abdominal pain, diarrhea, or vomiting); chronic urticaria that is not well controlled; and asthma, especially if not adequately controlled.<sup>8</sup> In my opinion, uncontrolled asthma is the one contraindication that is most important. Uncontrolled rhinitis, urticaria, and eczema simply make interpretation more difficult, but these conditions are not likely to lead to worse outcomes.

## HOW TO PERFORM

There are many things to consider when undertaking OFC to peanut.

## Location

As with any food challenge, the location of the peanut challenge (to diagnose or rule out IgE-mediated allergy) should be in a setting that has the capability to manage anaphylaxis. Theoretically, the risk of the OFC outcome is no different than the risk of performing subcutaneous immunotherapy to inhalant allergens (*i.e.*, anaphylaxis). Thus, it is reasonable to suggest that, if an office is equipped to administer subcutaneous immunotherapy, then it is equipped to perform OFC. The most recent anaphylaxis practice parameters contain information on the recommended equipment to have available in the office.<sup>15</sup> A recent work group report on infant food challenges to peanut also gives some extra guidance on equipment and medications for this specific patient population.<sup>10</sup> For example, oxygen should be delivered through a face mask, and thus infant- and child-sized masks should be available, and cuffs should be sized and available for infants and children to accurately measure blood pressure. In addition to appropriate emergency therapy, the office may consider having a digital scale that can measure to the 0.1-mg level and measuring equipment (tablespoon, teaspoon, *etc.*, down to one-eighth teaspoon) available to aid in measuring doses of peanuts, peanut butter, or peanut flour and/or protein if this is to be used. The OFC Work Group report<sup>8</sup> gives some guidance on whether challenges should be performed in the inpatient or outpatient setting. In the end, this is likely to come down to an individual and institutional decision.

## Material

The form that the peanut should be fed in is up to the clinician. For open challenges, giving the food in the natural form (*e.g.*, peanuts or peanut butter) offers the advantage of having the patient challenged to the same form that will be eaten in day-to-day life. However, using peanut flour and mixing it into a vehicle, such as apple sauce or pudding, may be helpful in some cases because it somewhat masks the taste; also, peanut flour can be measured in more precise amounts (if that is deemed important). Typically, challenges with peanut flour are reserved for research protocols, in which exact amounts and blinding are important. Various forms of peanut with proposed amounts of protein are given in Table 2.

## Goal Dose

The goal maximum and cumulative doses of the challenge are in some ways arbitrary. The maximum and cumulative dose in a challenge done to diagnose or rule out allergy should be large enough that it identifies all patients with peanut allergy (*i.e.*, one does not want to have a false-negative challenge due to not

Table 2 Protein content and measuring guide for peanut products\*

| Peanut Form          | Protein, % | Simple Measurement Dosing         |
|----------------------|------------|-----------------------------------|
| Peanuts, dry roasted | ~24        | 1 oz (~28 peanuts) = ~7 g protein |
| Peanut butter        | ~22        | 2 tablespoons = ~7 g protein      |
| Peanut flour         | ~50        | 14 g (~1/2 ounce) = ~7 g protein  |

\* From Ref. 28.

reaching a patient's threshold dose). In addition, it should allow the patient and the practitioner confidence that the patient will not react to a larger amount if more is eaten "in the field." The PRACTALL guideline<sup>9</sup> for double-blind challenges suggests a cumulative dose of ~4.5 g of peanut protein, with a final dose of 3 g. It is acceptable to challenge beyond this dose, but challenging to a dose lower than this may risk not reaching a threshold amount. Practical goal dose amounts for various forms of peanut are provided in Table 2. For peanuts, the weight for an individual peanut varies by size. However, if an average peanut kernel weighs ~1 g and is 24% protein, then ~28 peanuts would allow for ~7 g of protein.

## Starting Dose and Schedule

In selecting a starting dose and schedule, the clinician should consider a starting dose that is not likely to lead to a reaction in most patients and a dose and a schedule that will be feasible in an outpatient setting. There has been a great deal of research in determining the dose that would cause 1, 5 or 10% of the peanut-allergic population to react, called the Eliciting Dose (ED)01, ED05, ED10, respectively.<sup>16</sup> For example, the ED05 for peanut is estimated to be 1.5 mg of peanut protein.<sup>17</sup> Thus, if a clinician were to start a challenge at this dose, it would be reasonable to expect that ~5% of those challenged would have a reaction. In one recent study, the actual percentage of patients who reacted to this dose was 2.1%.<sup>17</sup> One must understand that these estimates are obtained from studies that enrolled subjects who were known to be allergic to peanut. Thus, if one is doing a challenge in a lower-risk population (attempting to rule out allergy in patients who have a lower likelihood of having peanut allergy), it is reasonable to start at higher doses. For double-blind challenges, the PRACTALL report<sup>9</sup> suggests starting with a dose of 3 mg of protein. This would require measuring ~12.5 mg of peanut butter or 6 mg of peanut flour, which would require a digital scale.

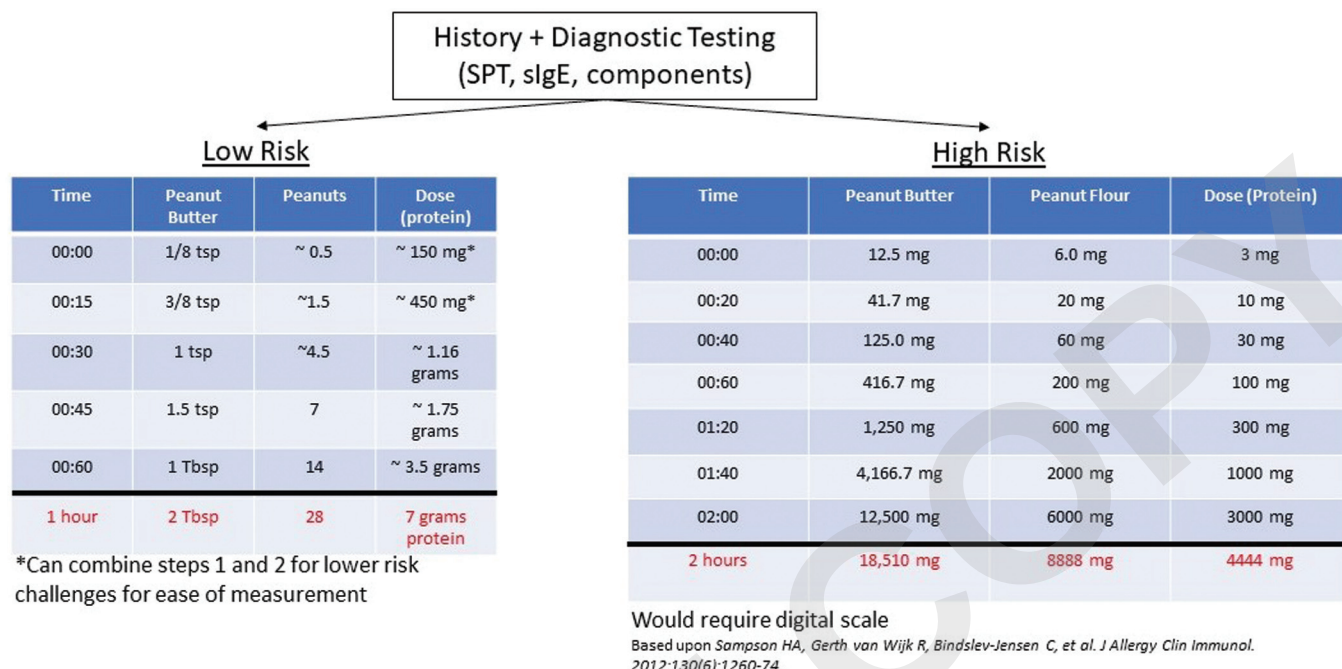


**Figure 1.** Proposed algorithm and dosing schemes for open peanut challenges.

Another OFC work group report acknowledges that prior European guidelines<sup>18</sup> suggest starting at very-low doses, such as 0.1 mg for peanut; however, the report notes that, if the challenge is being done in individuals are at lower risk, such as those typically being undertaken to prove or disprove allergy in an individual who is otherwise at low risk, then the practitioner can start at higher doses. Thus, patient selection is key to deciding on the starting dose. In the typical outpatient allergy clinic setting, most challenges undertaken are likely lower risk (compared with challenges in research studies that enrolled subjects known to have peanut allergy) and, therefore, can likely be started at higher doses.

Once the practitioner has selected the starting dose, he or she can determine the progression of the challenge by increasing the doses (*e.g.*, logarithmic), with each dose given at 15–20–minute intervals. The PRAC-TALL report<sup>9</sup> suggests a schedule such as 3, 10, 30, 100, 300, 1000, and 3000 mg of peanut protein at intervals of at least 20 minutes. This scheme would take ~120 minutes of feeding time. In low-risk challenges, it would be reasonable to modify this scheme for the outpatient setting. In my experience, peanut challenges in this low-risk setting can be carried out in 4–5 doses by using the natural form of the food (peanut butter or peanuts). Examples of dosing schemes are given in Fig. 1. No matter which scheme is chosen, the patient should be closely monitored throughout the procedure. Symptoms should be assessed throughout the challenge, and, ideally, symptoms and vital signs (heart rate, blood pressure, and respiratory rate) should be assessed before each dose.

## STOPPING THE CHALLENGE

There are many resources available to help define a positive oral challenge result, and some of these, *e.g.*, the OFC Work Group report,<sup>8</sup> even provide example forms for recording the challenge procedure and symptom scoring sheets. There is nothing unique to peanut challenge that should make it any different than for challenge to other foods. One point to note, however, is that peanut challenges are often carried out in children or adolescents who have been told to avoid the food for their lifetime. In my experience, this often leads to a great deal of anxiety in the lead up to a peanut challenge. Some patients have had symptoms of a positive challenge (*e.g.*, itching and vomiting) before the challenge procedure has even begun. Thus, it is important to gauge this level of anxiety before starting the challenge to have a better idea of subjective symptoms to expect during the challenge. There are various techniques to help identify subjective symptoms; the easiest of which is to extend the observation period to allow for symptom resolution before the next dose, which allows the patient to drink water. If the subjective symptoms cannot be overcome, then a blinded challenge should be considered as the next step.

## AFTER PASSING A CHALLENGE

If the patient tolerates all the doses without any signs or symptoms of a reaction (after an observation period of 2 hours postchallenge), this should rule out an IgE-mediated allergy. Based on this, the patient should be allowed to eat peanut in all forms *ad lib*. One report

suggests that, if a patient does not add the peanut into his or her diet after passing a challenge, then he or she may react at a later date if exposed to peanut.<sup>19</sup> Thus, it is reasonable to suggest keeping peanut in the diet in patients who have recently passed a challenge. There is no set amount that has been defined to accomplish this. Based on the Learning Early About Peanut (LEAP) allergy study, ingestion of a total of 6 g of protein (two 1-oz bags of Bamba (Osem Food Industries, Shoham, Israel) or 5 teaspoons of peanut butter) per week divided over three feedings is reasonable in infants and toddlers. Perhaps more would be needed in adolescents or adults, but this is not known.

## THE EXPOSURE CHALLENGE TEST

Many patients with food allergies have anxiety associated with their food allergy.<sup>20,21</sup> This anxiety can stem from fear of exposure to an allergen even if not ingested. This can be apparent even in casual settings, such as in lunchrooms, or at social events, such as birthday parties and baseball games. Results of studies have shown, however, that casual contact to peanut, such as wiping peanut butter on the skin of patients with allergy (even those with a history of anaphylaxis to ingestion), does not lead to systemic reactions.<sup>22,23</sup> For patients who are truly allergic and have this fear, one alternative to an oral challenge test is an exposure or proximity challenge test.<sup>24</sup> In this test, the patient, in the examination room, is exposed to peanut or peanut butter but does not ingest it. There is no set protocol for this; however, there is one reference that explains how this is done at one food allergy center.<sup>24</sup> In addition, one recent publication examined using this to improve quality of life.<sup>25</sup>

Anecdotally, this exposure challenge has been invaluable in allaying fears from patients at my institution. Here, I simply open a jar of peanut butter or a bag of peanuts in the room during the patient interview. After ~5 minutes, we bring the peanut product closer to the patient and continue the interview. After 5 more minutes, if we have peanut butter, I will wipe peanut butter on nonlesional skin and leave it on for 2 minutes. Although this can sometimes lead to some erythema, it often does not lead to any reaction at all and can provide the patient and family with reassurance that casual contact will not lead to systemic reactions.

## SUMMARY

Due to the recent increase in peanut allergy prevalence, clinicians who are caring for patients with food allergy should have a fundamental knowledge regarding a peanut allergy diagnosis. Although allergy skin testing and serum IgE testing can help to risk-stratify patients, these tests are not the criterion standard for a diagnosis of IgE-mediated food allergies. The double-

blind, placebo-controlled food challenge is the criterion standard; however, in clinical practice, the open food challenge is the practical alternative. This procedure can be instrumental in ruling out IgE-mediated peanut allergy in patients who are sensitized but tolerant and may be required for early introduction of peanut in individuals at high risk to have any true impact on disease burden in the population. In addition, OFCs can have a positive impact on the quality of life for both the patient and/or parent, and this may not matter whether they pass or react during the challenge.<sup>26,27</sup> Thus, it is imperative for allergists and other clinicians who are caring for these patients to have an understanding and comfortability in performing these challenges.

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