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Oral Food Challenges: Special Considerations

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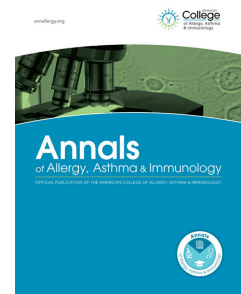
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Title Page

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Oral Food Challenges: Special Considerations

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Abbreviations/Acronyms:

SPT: skin prick test

OFC: oral food challenge

sIgE: specific IgE

FPIES: Food protein induced enterocolitis

BM: baked milk

BE: baked egg

NSAID: non-steroidal anti-inflammatory medication

PVFM: paradoxical vocal fold motion

PFAS: pollen food allergy syndrome

FDEIA: food dependent exercise induced anaphylaxis

ACE: angiotensin-converting enzyme

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Tables: 3

Introduction:

Oral food challenges (OFC) play a vital role in the diagnosis of food allergy. History, skin prick testing (SPT), and serum specific IgE (sIgE) tests contribute to the probability assessment of having a food allergy, but do not allow for diagnostic certainty in confirming or de-labeling a food allergy.¹ Accurate and cost-effective tests to diagnose food allergy are still required.²

Given the current need for OFCs, groups have undertaken efforts to standardize OFCs³⁻⁷ and an updated OFC work group report has been recently published.⁸

There are common features to any OFC. The risk benefit determination is a key component and drives the decision to offer the OFC. This determination requires consideration of multiple factors, which are summarized in Table 1. While these aspects apply to each OFC, this review will focus on some special considerations in these domains.

Why is the OFC being offered:

Probability of having a food allergy

In clinical practice, most OFCs have historically had a low probability of inducing an allergic reaction because of selection of patients who are likely not allergic or have outgrown their allergy (e.g. remote or unclear history of reaction, low SPT or sIgE). An American survey of 5 centers found only 14% of pediatric patients had a failed (positive) OFC.⁹ An international multi-center survey of 1634 children undergoing hospital-based peanut OFCs found 32% of patients had a failed (positive) OFC. The amount of peanut required to elicit a reaction was 20mg (95% CI: 15,25), corresponding to approximately 1/10 of a peanut, for 10% of the patients.¹⁰

In contrast, the probability of a failed (positive) OFC is higher in OFCs intended to

provide a definitive diagnosis in patients highly suspected of being food allergic (confirmatory OFC), or to determine the level of sensitivity (or the threshold) for patients with known or highly suspected food allergy. In oral immunotherapy treatment (OIT) protocols from a single US center, 73% of the 1445 patients reacted to ≤ 500 mg food protein (equivalent to approximately ≤ 2.5 peanuts) and 10% of patients reacted to less than 1.52mg (95% CI: 0.89,2.15) protein¹¹, corresponding to approximately 1/130 of a peanut. The finding that confirmatory and threshold-discovering food challenges have a high probability of allergic reaction and trigger allergic reactions at low allergen doses is especially important as OFCs are offered in clinical practice to establish food allergy prior to the initiation of food allergy treatments.

Severity of an allergic reaction

A recent prospective study of 5062 pediatric OFCs showed that the prevalence, severity, and treatment of allergic reactions depended on the indication with the most severe reactions occurring when the indication was to discover the threshold to start oral immunotherapy.¹² In 74 patients with food allergy confirmed for a clinical trial, 39% were treated with epinephrine.¹³ Therefore, the highest severity of OFC reactions tend to occur in the patients who are also at the highest probability of being allergic. However, on an individual basis, it can be difficult to predict the severity of food allergy reactions, therefore it is important to closely monitor patients during OFC protocols for symptoms and signs of allergic reaction. Some foods are associated with severe reactions including peanuts, tree-nuts fish, shellfish and milk,⁴ wheat¹⁴ and sesame.¹⁵ It is worthwhile to note that in general, skin testing, and sIgE levels do not correspond to reaction severity.⁴ Table 2 summarizes some important considerations of probability, severity and the dose threshold of reaction in OFCs.

OFC Dosing considerations in low probability versus high probability of allergy

Differences in the probability of reaction, eliciting dose and severity of reaction result in different advice as to how to conduct the OFC. The starting dose of an OFC may take into account prior clinical history.⁵ The top dose may vary by the goal of the OFC. A final dose of about 3000mg of food protein is endorsed to determine reactivity with a low false-negative rate.⁴ This amount of food will typically correspond to an age appropriate serving size. However, some OFCs are designed to determine the allergy threshold in individuals who very likely have a food allergy. For example, in the largest OIT study conducted, eligible participants had to react to ≤ 144 mg of peanut protein,¹⁶ (for reference one peanut kernel contains about 200mg peanut protein); therefore, the top dose administered was not sufficient to determine whether or not a full serving of the allergen would trigger a reaction.

Which Food should be challenged?

Special Considerations for Baked Milk and Egg OFCs

Many milk and egg allergic children can eat baked milk (BM) or baked egg (BE) without an allergic reaction due to the heat denaturing of conformational epitopes and subsequent decreased sIgE-binding capacity.¹⁷ Individual studies have produced guidance for sIgE and SPT testing, but universal cut-offs are lacking¹⁸ and an OFC is often needed to assess tolerability.

The purpose of the BM or BE OFC is especially relevant. Some clinicians advise for sub-threshold introduction of BM or BE over weeks at home to introduce some into the diet, while others advocate for a full serving, medically observed OFC to dichotomously prove allergic or not allergic before home ingestion because severe allergic reactions can occur, as was recently reviewed.¹⁹ Furthermore, the motivation of the BM or BE OFC may be to possibly shorten the

duration of allergy to regular milk and egg.^{20,21} In observational studies, children who are regularly eating BM and BE have immunological changes similar to those found in milk and egg OIT trials.^{19, 22-24} New randomized controlled trial data demonstrated that BM-tolerant children eating BM did hasten the development of tolerance to liquid milk.²⁵ In this trial 37/42 (88.1%) children eating BM became tolerant to liquid milk, versus 28/42 (66.7%) who were avoiding all forms of milk ($p=0.018$).

The type of food challenge material is important in BM/BE OFCs. Clinic supplied products can control for the baking time and ingredients. Typically, the food challenged is BM or BE in a wheat matrix baked at 350° F/180° C for 30 minutes, although the key is that the item is thoroughly cooked. Wheat flour-based BM and BE products may decrease sIgE-binding over other flours and may be more likely tolerated.²⁶ The Jaffe Food Allergy Institute at Mount Sinai recipes are readily available and each serving of wheat-based muffins contain 1.33g of milk protein and 2g egg white protein.¹⁷

Patients who undergo BM and BE OFC need educational support to successfully incorporate these foods into their diet including which foods they can and cannot eat. The amount of BM/BE allowed in the diet has varied. Up to three servings a day have been advised^{23,24} and others have advised at least once a week.²⁷ The form of BM or BE can be progressed with time to lesser cooked forms. In a recent trial, 42 patients who tolerated BM muffins for 6 months were challenged under medical supervision to baked cheese and 39/42 tolerated.²⁵ Given the numerous considerations and differing advice in BM and BE OFC, an AAAAI workgroup of the BM and BE approach to milk and egg allergy is underway.

Special Considerations for Tree Nut OFCs

Historically, children allergic to one nut have been tested to all nuts and often have been

given the advice to avoid all nuts. Due to the recognition that early dietary introduction and maintenance of peanut is tolerogenic versus prolonged avoidance²⁸, there is movement to avoid only the nuts to which the child is actually allergic, as was recently reviewed.²⁹ Almond in particular may be very likely to be tolerated and may warrant a stronger consideration to offer an OFC.³⁰ In a series of 590 patients who underwent clinical OFCs to almonds, there were just 30 (5%) failures and 15 (3%) indeterminates. These results contrast to 31% failed (positive) OFC for other foods in their institution.

Special considerations in where and how to perform an OFC

The decision of where to offer an OFC is influenced by multiple factors. Suggestions have been published using clinical features (e.g. history of asthma, allergy testing results) to select home, office, medically intensive settings, or to defer OFCs.³¹ Patients with factors known to be associated with death from anaphylaxis should also be considered at risk of severe reaction [Table 2]. Patients with asthma are more likely to need epinephrine in a failed (positive) OFC and should be carefully triaged and have their asthma very well controlled.³¹

There is a distinction between the chances of reacting to an OFC (the probability of reaction), and the chances of a severe reaction (Figure 1). The possibility of an allergic reaction, and that it can be severe, necessitates controlling risk factors for a severe reaction [Table 2] prior to OFC and medical expertise and appropriate equipment to treat anaphylaxis.³²

In addition to considerations of risk of reaction and severity, the possibility of a delayed allergic reaction or the effect of cofactors also influence the location and protocol of OFCs.

Delayed Reactions:

Delayed Mammalian Meat Allergy (alpha-gal)

Delayed mammalian meat allergic patients have an IgE-mediated allergy to alpha-gal, a polysaccharide in mammalian meat. The delayed nature of this allergic reaction (i.e., symptoms classically start 3-6 hours after ingestion) creates a special circumstance for OFC protocols, as was recently reviewed.³³ One dose OFCs to meat with a prolonged observation time have been used, but these may not be appropriate for patients with a history of anaphylaxis or risk factors for severe reaction [Table 2]. There is also the complicating factor that the clinical reactivity to meat can be inconsistent and influenced by the food and cofactors. For example, it has been reported that pork kidney may induce an allergic reaction due to alpha-gal sensitization within an hour, or that these OFCs should use cofactors (e.g. NSAIDS) to lower the threshold and more reliably elicit the reaction. Furthermore, it has been recommended that alpha-gal OFCs are performed by experienced allergists on an inpatient basis with emergency response measures in place.³⁴

Food protein induced enterocolitis (FPIES)

Food protein induced enterocolitis (FPIES) is a rare, non-IgE-mediated, food-induced allergic disease, and the acute form of the disease is characterized by delayed, repetitive vomiting along with paleness, extreme lethargy and/or diarrhea.⁷ Symptoms typically appear in infancy and resolve in early childhood, though rarely, new onset disease may appear in adulthood.⁷ A chronic form of the disease is much less common than acute FPIES and typically appears in the first 3 months of life secondary to cow's milk ingestion.⁷

There are no confirmatory tests for FPIES apart from an OFC. Universal agreement

regarding a standard approach to conducting an FPIES OFC is lacking. International consensus guidelines recommend giving 0.06-0.6g food protein per kg body weight to a maximum of 3g of protein (no more than 10g of total food by weight) with an observation period of at least 2 to 3 hours.⁷ The food serving may be given as a single serving or divided into 3 equal servings over 30 minutes. If the initial dose is low (e.g. 0.06 g/kg), then a full serving may be given after the initial observation period with additional observation recommended. In patients with detectable sIgE to the challenge food, a more gradual administration of the challenge food may be considered, similar to an approach that would be used for IgE-mediated OFCs and with a prolonged observation time.

A variety of other approaches have been published. The approaches vary by the dose administered, observation time, and progression to full serving size, but all have the unifying objective to give the lowest possible dose that is likely to trigger a reaction based on the presumption that higher doses may lead to a more severe reaction. Wang, et al. based their total dose on a standard, age-appropriate serving size, giving 1/3 of the total serving under observation and increased to the full serving at home.³⁵ With this approach 7.7% of challenged patients reacted at home with diarrhea or less commonly vomiting within the first few days of home dosing. Barni, et al. reported that 25% of the total serving was sufficient to trigger a reaction in their patient cohort.³⁶ Others have reported a minimum reactive dose of 0.15 g/kg body weight.³⁷ Infante, et al. performed FPIES OFCs over several days with less than 50% of the total serving given on day 1, followed by the full serving on day 2; no reactions were elicited with the second day of dosing.³⁸ This group's 2-day protocol for fish FPIES OFCs showed that 81% of reactors had a reaction on the first day of the challenge after receiving 25% of the total serving.³⁹

The cumulative experience from these studies would suggest at least 0.15 g/kg of protein

or 25 to 33% of a standard serving is necessary to trigger a reaction for the majority of patients. The majority of FPIES OFC literature is based on retrospective review from single center experience. Prospective, multi-centered research is needed to refine and standardize the FPIES OFC protocol with particular focus on establishing minimum reactive doses across populations, pre-challenge risk stratification, and post-challenge dietary advancement when a full serving is not challenged.

Guidelines suggest treating a reaction with rehydration (oral or intravenous (IV)), ondansetron (IM or IV) and consideration of administration of methylprednisolone for severe reactions (i.e. >3 episodes of emesis, with severe lethargy, hypotonia, ashen or cyanotic appearance).⁷ IV fluid rehydration may be needed in more than 50% of failed (positive) OFCs,³⁶ though large studies have not been performed. Katz, et al. reported exclusive oral rehydration in a sample of 24 milk-FPIES reactive infants.⁴⁰ Higher risk FPIES OFCs may be considered in more experienced challenge centers, although inpatient hospital admission is not typically necessary. If staff is uncomfortable starting an IV, then a care plan algorithm may include the use of IM ondansetron and ready access to emergency medical services if transfer to an acute care setting is necessary. At the time of writing, no mortality has been reported secondary to FPIES. Although reacting patients may appear quite ill, they rarely develop hypotension, and full recovery should be expected.

Data are limited regarding tolerance of BM or BE proteins in non-IgE mediated food allergy. Small case series have shown tolerance for the minority of children with eosinophilic esophagitis (EoE) and some children with FPIES, but larger studies are needed before definitive recommendations may be provided.^{7, 41}

Cofactors

There are multiple factors which can reduce the threshold of an allergic reaction, meaning reduce the amount of food it takes to elicit symptoms and signs. The best described co-factors are exercise and NSAIDs, but concomitant pollen allergy, alcohol, stress, fatigue, menstruation, infections, medications (antacids, cannabis, ACE-inhibitors) have all been described.^{42, 43} Cofactors may be interchangeable, rather than specific to the reaction. For example, food dependent exercise induced anaphylaxis (FDEIA) can be more easily elicited with NSAIDs.⁴⁴ Furthermore, FDEIA can be elicited without any exercise by giving high doses of the food at rest.⁴⁵ Therefore, in FDEIA, the patient has an IgE-mediated allergy to the food at high doses which they do not normally encounter in their diet, but when they have exposure to cofactors the allergic reaction is triggered.

While there is no consensus OFC protocol to evaluate for FDEIA, in general the approaches are a food challenge, a cofactor challenge, followed by a combined food–cofactor challenge⁴³. Exercise has been described to be performed 30 minutes to 1 hour after the food challenge. Although exercise OFCs are the gold standard for FDEIA, they likely have lower sensitivity than typical OFCs. If the food-exercise challenge is passed (negative), there may be a need for further exercise or additional cofactors such as NSAID administration in combination with the food.⁴⁶ Exercise OFCs require full medical monitoring and equipment to treat anaphylaxis.

Incorporation of the Food

It is important to consider the risk of failure of re-introduction, because OFCs are time consuming and expensive. After a passed (negative) OFC, there may remain barriers to the

incorporation of the challenged food into the diet. A recent 3 year follow up of children who passed an OFC to peanut found that 9/28 had not introduced the food due to fear and/or aversion.⁴⁷ One trait which has been prospectively identified as associated with failure of re-introduction in children is a lack of interest in eating a new food.⁴⁸ Rarely, a patient may react at home after passing an observed OFC. This could be explained by either a higher dose triggering a reaction than was fed in clinic, or cofactors which lowered the triggering threshold. Food introduction may require psychological support in some individuals⁴⁷ or follow-up with consideration for repeat challenges.

Special considerations of OFC related to age

Infant Oral Food Challenges

Introduction of allergenic solids into the infant diet, especially peanut and egg, has proven beneficial for prevention of peanut and egg allergies in high risk infants.^{28, 49} Guidelines from national societies now emphasize safe early introduction of allergens starting at 4 months of age.⁵⁰ The unique characteristics of infants requires attention to the following considerations to be successful.

Conducting an OFC in an infant should take into account their unique feeding schedule.⁶ Typical OFCs recommend a 4-hour fast prior such that absorption is not delayed, but this will not always be possible with an infant⁵; therefore, a 2-hour fast with the last oral intake (e.g. breastmilk or a light breakfast) equivalent to approximately half a typical serving is suggested. Furthermore, scheduling the OFC within the infant's typical feeding routine and outside of usual sleep may maximize chances for successful ingestion.⁶

Feeding protocols for peanut have been derived from the Learning Early About Peanut

(LEAP) protocol.^{6, 28, 51} The recommended protocol administers approximately 4 grams of protein divided amongst 5 servings, with each serving giving a progressively larger amount.⁶ Similar approaches may be adapted for other allergenic solids, such as the approach outlined by Enquiring About Tolerance (EAT) investigators.⁵² Infants participating in the EAT trial were challenged to cow's milk, cooked egg, wheat, peanut, sesame seed (i.e. tahini), and whitefish if testing suggested sensitization (i.e. a SPT wheal diameter > 0 mm). Each food was challenged in a similar manner with five doses of food protein of 0.1, 0.25, 0.5, 1.35, and 2.0 g (≥ 6 months) with approximately 20 minutes between doses.⁵² For other foods, a similar process can be followed with an OFC dose of least 2 to 3 grams of total protein (in a format which will not pose a choking hazard) should trigger a reaction in the majority of infants.⁸

Assessment of an allergic reaction in infants requires more attention to the clinical exam compared to verbal patients. The infant should be well and concomitant allergic diseases should be maximally controlled.⁶ Coughing, irritability, and/or poorly controlled atopic dermatitis will interfere with OFC interpretation. Subtle symptoms of reactivity include ear picking, tongue rubbing and neck scratching.⁶ Potential signs of reactivity including increased irritability, clinginess, and feeding refusal are difficult to interpret because they may also occur in healthy infants. Cutaneous symptoms are the most common objective presentation of allergic reactivity in infancy, though a systemic reaction with or without cutaneous symptoms may occur.^{6, 53} As with other OFCs, in the absence of clearly objective allergic symptoms the clinician may consider repeating a dose of the OFC, delaying the next dose or may conclude the outcome is inconclusive and repeat another day.⁶ It has been suggested that if at least half of the OFC is ingested then that amount may continue at home and, if tolerated, be gradually increased to an age-appropriate, standard serving size of the allergen.⁶ Interpretation of infant vital signs requires

recognition of the ranges for infants⁶ as shown in Table 3. Obtaining a blood pressure in infants may be particularly challenging, and then the clinician must rely on other physical exam findings to assess for the need for volume expansion.

Treatment of an allergic reaction in infancy does not differ significantly from treatment of anaphylaxis in other age groups though there are several unique considerations.⁵⁴ It is recommended to place the infant supine in the caregiver's arms for assessment. As in other age groups, epinephrine should be administered in the mid-outer thigh at a dose of 0.01 mg/kg. An epinephrine auto-injector may be used, and a dose of 0.10 mg or 0.15 mg may be used, if available. Infant-sized equipment (e.g. face mask for supplementary oxygen) is required.

At the conclusion of the OFC, if the child tolerates the food without reactivity (i.e. a negative challenge), then it is especially important that the food is reincorporated into the infant's diet on a regular basis. A minimum amount of protein in the diet has not been identified, but approximately 6 grams of protein per week divided into at least 3 individual servings per week^{6, 51} was demonstrated to contribute to the prevention of allergy development²⁸ and a subsequent 12-month period of avoidance after 5 years of age was not associated with peanut allergy development.⁵⁵

Adult Oral Food Challenges

Adults may have food allergy which has continued from childhood or they can have adult-onset. A recent survey in the United States (US) found that 19% of adults believe they have a food allergy, about half have symptoms suggestive of allergy, and half of these adults developed the symptoms in adulthood.⁵⁶ In Europe, the estimate of adult food allergy as defined by symptoms plus sIgE sensitization ranged from 0.3% in Athens, Greece to 5.6% in Zurich,

274 Switzerland.⁵⁷

275 Adults may have co-existing medical conditions which affect risk/benefit of the OFC
276 such as cardiac disease, or they may be on medications which put them at risk of a more severe
277 allergic reaction such as non-steroidal anti-inflammatory medications (NSAID), β -blockers and
278 ACE-inhibitors.^{4, 5}

279 Adults may have non-allergic symptoms such as gas and bloating from FODMAP
280 (Fermentable Oligo-Saccharides, Disaccharides, Monosaccharides And Polyols) foods, or the
281 controversial non-celiac gluten sensitivity, or irritable bowel syndrome.⁵⁸ They may also be
282 more likely than children to have pollen food allergy syndrome (PFAS), which was recently
283 reviewed.⁵⁹ PFAS brings special considerations for both food selection and symptom
284 interpretation. The food, fruit or vegetable, needs to be intact and raw enough to have the
285 appropriate allergens and subjective mouth symptoms may be the targeted challenge outcome,
286 rather than an indeterminate symptom as in a typical food challenge.⁵

287 The interpretation of an OFC can be complicated in adults. As an example, upper airway
288 symptoms can be a sign of laryngeal edema from an allergic reaction or these symptoms could be
289 due to paradoxical vocal fold motion (PVFM)⁶⁰ which may require consideration for later
290 evaluation by spirometry or direct visualization of the vocal cords. Non-specific symptoms or
291 anxiety in adults may require double blind placebo-controlled food challenges.

292 There is conflicting evidence of whether increasing age may be a factor which leads to a
293 higher rate of failed (positive) OFCs. In 1643 hospital-based peanut OFCs in children age
294 predicted severity of reaction with anaphylaxis 3 times more common in teenagers than younger
295 children.¹⁰ However, in another large series of 2368 OFCs, age did not associate with failed
296 (positive) food challenges or their severity.³¹

Conclusion:

OFCs are required for definitive diagnosis of food allergy and many can be safely performed in the office setting. Nuance exists with respect to conducting the OFC in specific populations (e.g. infants versus verbal children versus adults), but the unifying characteristic across patients is gradual administration of allergen to approximate a full-serving of the food being challenged along with careful observation for objective symptoms of reactivity. Because of the risk of anaphylaxis, patients undergoing an OFC must be monitored closely with objective symptoms treated appropriately.

Protocol variations may be needed depending on the risk of reaction. For example, confirmatory challenges, modifying co-factors such as exercise or delayed reactions to mammalian meat may require dosing modification, prolonged observation, or additional interventions. Most FPIES OFCs may also be performed in the clinic setting but require additional planning for treatment of a reaction since patients with FPIES will not respond to epinephrine and will improve with rehydration (IV rehydration may be necessary) and ondansetron. After a successful OFC, guidance is required to successfully incorporate the food into the diet.

319 Tables

Table 1. Considerations for Oral Food Challenge	
Consideration	Details
Who is undergoing the OFC?	Age: Infants, Children, Adults Consideration of contraindications or modifications due to comorbidities: e.g. intercurrent illness, asthma control, medications
Where to perform the challenge?	Home Introduction, Office or Hospital
What food will be challenged?	Form of the food (baked (egg/milk), raw (pollen food allergy syndrome)) Amount of food (usually a serving size) Cross reactive foods (e.g. tree nuts)
Why is the OFC being performed?	To rule out food allergy in someone considered to now be likely to tolerate the food To provide a definitive diagnosis of food allergy in someone considered at high probability of food allergy To discover the dose threshold of allergic reaction in a person with proven To attempt to reduce dietary restriction in someone with multiple allergies
How will the OFC be performed?	Starting dose Time intervals between doses Criteria to stop the food challenge (subjective/objective symptoms) Observation time: Assessment of immediate or delayed reaction Cofactors: NSAIDs, exercise, Intravenous line placement prior to OFC
Post OFC advice	Advice to introduce the food routinely: which form, how often Will they eat the food? Consider follow-up/ psychological support

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Table 2. Selected factors contributing to the probability, severity and threshold of allergic reaction in Oral Food Challenges		
Risk/Probability of Allergic Reaction	Severity of Allergic Reaction (Factors associated with fatal or near fatal allergic reaction)	Factors which may reduce the threshold of allergic reaction
High skin prick test size, elevated sIgE	Patient Factors: Asthma, intercurrent illness	Medications: especially NSAIDs, but also antacids, ACE-inhibitors, β -blockers
Recent history of reaction	Food: Peanut, tree nuts, fish, shellfish, wheat, sesame, and milk	Illness
Research/Confirmatory OFC (due to selection of patients more likely to be allergic)	Procedural factors: Delayed use of epinephrine	Exercise
	Upright posture during anaphylaxis may contribute to cardiovascular compromise	Empty stomach (due to rapid absorption)
	Research/Confirmatory OFC (due to selection of patients more likely to be allergic)	Research/Confirmatory OFC (due to selection of patients more likely to be allergic)
		Recreational drugs: alcohol, cannabis
		Concomitant pollen allergy,
		Physiological factors: e.g. stress, fatigue, menstruation

Table 3. Infant Vital Signs	
Hypotension (age 1 to 12 months)	SBP <70 mm mercury
Tachypnea (age 2 to 12 months)	>50 breaths per minute
Tachycardia (age < 2 years)	>160 beats per minute

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Figure legends

Figure 1. The probability of an allergic reaction and probability of a severe reaction are considered when offering OFCs, as illustrated by 4 outcomes of 25 OFCs. In **Panel A**: The probability of an allergic reaction (failed/positive OFC) is the same but the probability of a severe reaction is higher in i.). In **Panel B**, the probability of an allergic reaction is higher in i.), but the probability of a severe reaction is the same. See text and Table 2 for risk factors for a positive OFC and risk factors for a severe allergic reaction. Legend: white: negative OFC, orange: failed (positive) OFC, red: positive OFC (severe allergic reaction).

Figure 2. The risk assessment of the OFC influences the protocol of the OFC.

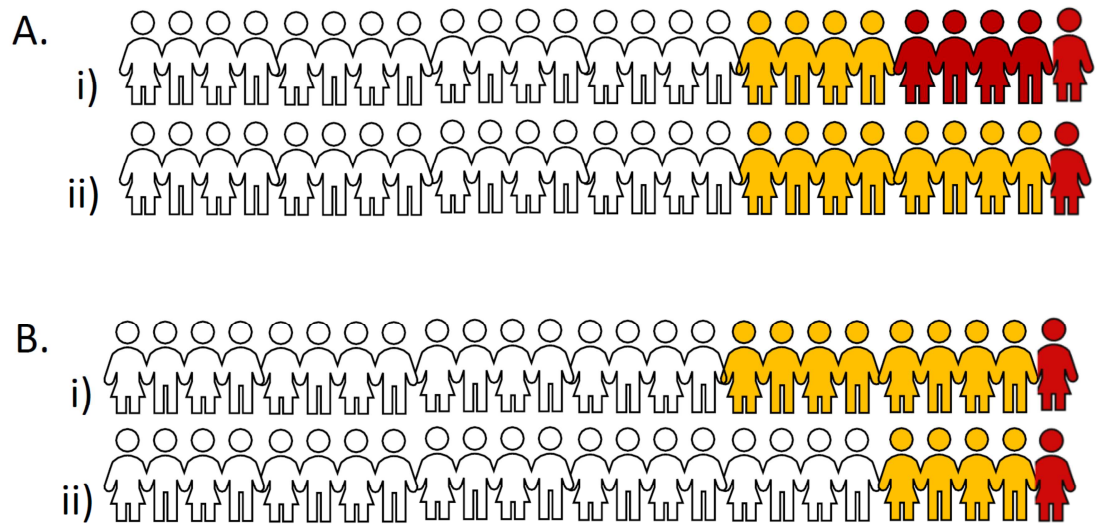


Figure 1.

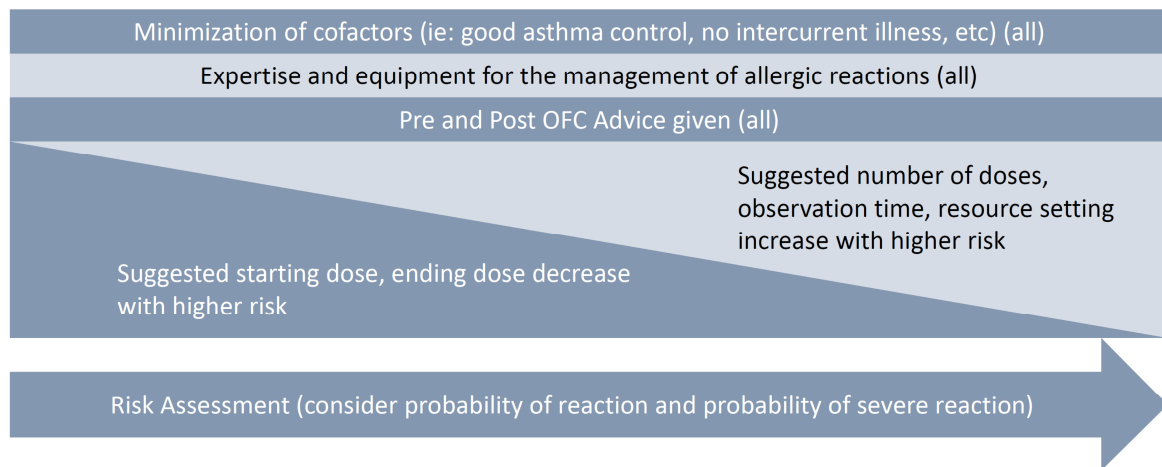


Figure 2.

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