

Pearls and pitfalls of food challenges in infants

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ABSTRACT

An oral food challenge (OFC) is considered the diagnostic criterion standard procedure for evaluation of a suspected food allergy in patients of any age. This can be accomplished as either an open or a blinded challenge. In recent years, the open OFC has become an acceptable and practical office-based practice. With the advent of new early peanut introduction guidelines, there is a critical need to potentially perform OFC in very young infants between the ages of 4 and 12 months of life. Experience from multiple recent randomized controlled clinical trials indicates that such OFCs are both safe and feasible, although the extent to which providers in the clinical setting are comfortable and experienced with OFCs in this population is unclear. This review detailed the essential features of performing an OFC in an infant to help guide the practicing allergist in how to set up his or her office and best accomplish this very important procedure.

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WHY ARE ORAL FOOD CHALLENGE IN INFANTS IMPORTANT?

Diagnosing a food allergy can be complex, in particular, with regard to patients who present with less than clear-cut symptoms and with multiple sensitizations. The important aspects in making a diagnosis are to obtain a thorough history that details what may have been eaten and which symptoms developed along what timeline. Based on the history, skin and/or serologic immunoglobulin E testing may be indicated¹ Whereas, typical symptoms of immunoglobulin E (IgE) mediated food allergy are straightforward and sensitization is easy to detect in that context, the diagnosis becomes more difficult to make when the history and sensitization data are discordant, the patient has sensitization without a history of symptomatic ingestion, or has a history of symptomatic ingestion without sensitization. In these circumstances, oral food challenge

(OFC) is the criterion standard diagnostic test.^{1,2} Although OFC is commonly performed in adults and children, its use in infants has been more guarded. However, analysis of more recent data has emerged that OFCs can be performed as safely and routinely as OFCs in older children.^{3–10}

Performing OFCs in infants has taken on new importance given that early peanut introduction recommendations are predicated on robust access to providers willing to perform OFCs in infants.¹¹ However, such OFCs may still be met with reservation from some providers.¹² Use of OFCs in this population can help confirm or refute the significance of food sensitization to prevent misdiagnosis. Historically, this population has been very cautiously considered for OFC for a number of reasons. Infants are nonverbal, very small, have highly specific vital sign ranges and varying degrees of cooperation with being fed; therefore, assessing infants during an OFC may be more difficult relative to an older child or an adult, even for an experienced pediatric allergist. Although no specific data support that infant OFCs are unsafe or infeasible, there is some concern regarding both these issues.¹³

DEFINING THE POPULATION

Infancy is commonly defined by the American Academy of Pediatrics as a child <12 months of age,¹⁴ although there may be other considerations for defining very young children, either by weight or by verbal and/or developmental ability (including considering infants and toddlers as a single unit compared with older, more verbal children). A recent American Acad-

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emy of Allergy Asthma and Immunology (AAAAI)¹³ workgroup report on OFCs in infants defined the infant population based on age, but a more recent expert consensus paper provides rationale with regard to considering the infants and toddlers as a singular unit (Greenhawt et al, submitted).¹³

There are limited U.S. data regarding performing infant challenges. Robust data from prevention trials exists, but there is no registry that describes the routine office-based experience with OFCs in infants.¹³ To date, the one known OFC-related fatality was reported in a noninfant age group.¹⁵ Data from a recent AAAAI survey denotes that 93% of 273 allergists surveyed routinely saw infants, and, in the past 12–18 months, 39% of these respondents reported a specific increase in referrals of 4–11-month-old infants for evaluation of early peanut introduction; however, 71.2% reported deferring challenging these infants, despite 94.8% reporting that their office offered OFC. Thus, there may be barriers to performing OFCs in infants (Griewe et al, AAAAI workgroup report, submitted).

OFCs IN INFANTS 101: PRIORITIZING THE IMPORTANT (BASIC) STUFF

OFCs in infants are like all other OFCs, and there are few specific technical pearls to their conduct that differ from OFC in other ages. The patient needs to be assessed, vital signs monitored, food ingested, and symptoms (if present) treated. Providers should still be following established guidelines and recommended operating procedures for typical OFC. The main concern is the logistical setup, to ensure a safe environment, an appropriate feeding vehicle, and a recognition of how a reaction may manifest in this age group and be treated.¹⁶ As with any challenge, there should be an organized and systematic approach. Providers should have a clear indication to conduct the challenge (e.g., this is a child who qualifies for in-office evaluation under addendum 1 of the National Institute of Allergy and Infectious Diseases guidelines,¹¹ or this is a child with multiple food sensitizations in the setting of eczema, *etc.*). A prechallenge call is recommended to be placed to the family a day or two beforehand to make sure that the family is still planning to come and to document that the child is well and not having any major health issues that could affect the OFC interpretation.^{13,16} The caregivers should also be counseled as to how the procedure will unfold in terms of timing and the sequence of events, and if the caregiver is responsible for any food preparation (with preparation instructions given if that is the case). It is strongly recommended that informed consent be obtained to document the process.

The office setup is a bit more nuanced in this age group versus with OFCs in older children. Foremost,

appropriate portion sizes for age and appropriate vehicles and/or food forms are needed for the infant. Only use mixing vehicles that the child has previously tolerated and make sure that soft or puree forms of foods are being used. Avoid items that pose choking hazards, such as peanut or tree nut kernels.¹¹ It is recommended to have a discussion with the family ahead of time as to who will provide these items. As with other OFCs, a dedicated room for the OFC is needed for ~4–6 hours, and the procedure should be planned for a time of day when the infant is normally awake and alert (e.g., avoid performing this around a nap time if possible, so the child can have the best chance of being alert and interested in feeding).^{13,16} As well, having some washable toys or other entertainment and/or distraction for the child is also recommended.

OFCs in infants (or any age) should only be conducted in a monitored setting, in plain sight of staff at all times.¹⁶ It is recommended to have a predesignated covering nurse and medical provider, with preassigned roles for who conducts the OFC, assesses for symptoms, and administers any treatments. It is highly recommended to have both a clear, written stopping criteria and a treatment plan,¹³ including how to transfer the patient to the emergency department in the event more advanced care is required. The large clinical trials for food allergy prevention, treatment, and prevalence that involve OFCs in infants have all had such features.^{3–8} As well, an OFC should only be attempted in an infant who is well, without signs of any acute or chronic illness that could lower the child's threshold to react or increase the risk of a severe reaction. This is why, within 48 hours of the OFC, there should be documentation of a discussion that verifies that the infant has been well and for the family to contact the office if that changes. If the child has asthma and/or eczema, then these must be under good control at the time of the OFC. Concomitant medications that could interfere with the interpretation of the procedure, such as antihistamines and short-acting β -agonists, should be discontinued.^{13,16}

HOPING FOR THE BEST BUT PREPARING FOR THE WORST: MEDICATION SETUP AND DOSES

The OFC is a safe procedure; however, there is always the chance that a patient could react and that such reactions could result in anaphylaxis.^{1,16} Therefore, ensure that resuscitative medications are on hand and immediately accessible during the procedure. Of all things to consider in performing OFC in an infant, the forethought for how to treat an infant is most paramount. Epinephrine must be available.¹⁷ Epinephrine is dosed at 0.01 mg/kg and is available in an

Table 1 Example medications and dosing for treating infant anaphylaxis*

Medication	Dose	Route
Epinephrine (1:1000)	0.1–0.15 mg (0.01 mg/kg)	Intramuscular
Cetirizine	2.5 mg	Oral
Diphenhydramine	1 mg/kg	Oral
Ranitidine	5 mg/kg	Oral
Prednisolone	1 mg/kg	Oral
Racemic epinephrine	0.05 mL/kg	Nebulized
Albuterol	0.05–0.15 mg/kg (maximum, 1.25 mg/dose)	Nebulized

*From Hughes HK, and Kahl LK. Johns Hopkins Hospital. *The Harriet Lane Handbook: A Manual for Pediatric House Officers*. Philadelphia, PA: Mosby Elsevier; 2018.

ampule that can be drawn up by syringe or *via* an autoinjector at either a 0.1-mg or a 0.15-mg dose. Either is an acceptable option.¹⁸ If using an ampule and a syringe, then the dose should be drawn up in advance of starting the OFC and the needle length should not exceed 0.25 cm to avoid the potential to strike bone. Irrespective of the epinephrine source, it is crucial to make sure that an accurate weight of the patient has been taken.

For those unfamiliar with pediatrics who may still conduct OFC in an infant, medications are very tightly dosed in mg/kg. Other medications that should be available include a liquid form of an H₁ antihistamine, either a short-acting agent such as diphenhydramine (12.5 mg/5 mL concentration, dosed at 1 mg/kg), or a long-acting agent, such as cetirizine or loratadine (both come in 1 mg/mL concentrations and are dosed at 2.5 mg in children <6 years of age, including infants). Additional medications to consider include albuterol administered in a nebulized form (1.25 mg solution in 3 mL of saline solution or one nebulized treatment ampule) for bronchospasm, a liquid H₂ antihistamine such as ranitidine (15 mg/mL, dosed at 5 mg/kg), and racemic epinephrine for any stridor development (2.25% solution, 0.05 mL/kg in 2.5 mL of saline solution). Although the benefits of corticosteroids in acute anaphylaxis management are debatable, some providers may wish to consider liquid prednisolone (15 mg/5 mL, dosed at 1 mg/kg).^{17–19} As is the case with epinephrine, it is recommended that all emergency medications are drawn up in advance of the OFC. A dosing range of potential medications is provided in Table 1.

The decision to place an intravenous (IV) before starting an OFC is individualized. Some tertiary centers elect to do this as a matter of routine, whereas others are more selective as to when to place IV.^{13,16} Most of the large trials^{3–5} that involve OFCs in infants have been conducted without IV access in place. For private offices, this will likely be a very highly individualized process. It is unclear how often an IV is used

for fluid resuscitation or medication administration in OFCs, but access can be useful in infants with anaphylaxis who evolve to hypovolemic shock. The dose for an IV fluid bolus in an infant is 10 mL/kg of 0.9% normal saline solution.¹⁷

There should also be a prespecified written treatment plan in place before starting the OFC that identifies how selected symptoms will be treated.¹³ This should specify the dosage of each medication to be potentially used and be at the bedside where the procedure is being conducted so that the treating provider can rapidly access this information if needed. Some centers and offices may have premade kits dedicated for treatment purposes kept at the bedside to also facilitate treatment.

OFC DOSING STRATEGIES IN INFANTS

Open OFCs are appropriate and sufficient for infants.^{3–5,11,13} Outside of research, a double-blind challenge is unnecessary in this age group. Infants should only be given soft, pureed, or dissolvable food forms that pose no choking hazard and that are easily eaten by someone with still-developing oral motor skills to prevent gagging and/or choking attributable to poorly developed feeding skills from being misinterpreted as a sign of a reaction.^{11,13} Use of a mixing vehicle, something that has been previously tolerated and is a familiar flavor and texture, is also helpful. Three other issues must also be considered. The first is to have alternatives available in case the infant rejects the initial vehicle choice. The second is to allow for ample time to feed; one can aim for a 15–20-minute interval between doses, but the speed at which the infant may eat his or her dose is cooperation dependent! The third is to choose an age-appropriate dose. These are clinical challenges and only require 3–4 g of total protein (*e.g.*, for peanut butter: 1/8, 1/4, 1/2, 1, 1.5 teaspoons).¹³ For a routine clinical challenge, the emphasis should be to feed an age-appropriate portion size, and, if in question, then the portion size should supersede the protein

Table 2 Infant vital sign pearls*

Vital Signs	Ranges
Blood pressure, mm Hg	Systolic 72–104/diastolic 37–56, ages < 12 mo; hypotension is <70; systolic 86–106/diastolic 42–63, ages 1–2; hypotension is <70 + (age × 2)
Respiratory rate, breaths/min	30–53 for ages <12 mo; 22–38 for ages 1–4 y
Heart rate, beats/min	100–190 (awake), 90–160 (asleep) for ages <12 mo; 98–140 (awake), 80–120 (asleep) for ages 1–2 y

*From Ref. 20.

content. It is also important to use one's judgment. The infant may not eat the entire portion, although he or she may eat enough to rule in or rule out a diagnosis. The ordering provider needs to carefully consider such circumstances.

VITAL SIGNS ARE VITAL! CRITICAL PEDIATRIC VITAL SIGN CRITERIA

The other highly crucial aspect of performing OFCs in infants is in obtaining accurate vital signs. Vital signs in infants and children, naturally, are different than those of adolescents and adults (Table 2). Moreover, vital signs vary across young ages, and it is recommended that providers unfamiliar with basic pediatric care seek normal age-based vital sign references from available sources. In particular, infant vital signs have some baseline intricacies that require having familiarity with before performing OFC. Systolic and diastolic blood pressure measurements run much lower than the typical adult at baseline. Moreover, cuff size to measure blood pressure is very critical; the cuff must be appropriately sized for the infant or the blood pressure readings will be wrong. A small adult or even a standard child-sized cuff is not appropriate, providers should obtain an infant and toddler-specific cuff. Although automated blood pressure machines can accurately measure infant blood pressure and heart rate, providers may want to consider a manual cuff backup because these machines may struggle to detect readings in a crying infant.²⁰

Respiratory rate in pediatrics also has a particular importance. Whereas, a common hospital floor convention for an adult respiratory rate may be 20 breaths/min, infants normally breathe at nearly twice this rate, and the range will fluctuate based on the child's age. The quality of the respirations is equally important. When assessing the infant before, during, and after the challenge, one must note the presence of any use of accessory muscles of breathing (e.g., sternocleidomastoid muscles or other muscles of the neck, chest, or torso that can be incorporated to assist the work of breathing). Use of accessory muscles, often denoted by their obvious movement or the appearance of parts of the chest wall that appear to "retract" with inspiration (e.g., retractions) or other pulling

of muscles with breathing or "belly-breathing" are ominous signs of respiratory distress in an infant. Whereas these compensatory muscles can temporarily help an infant with the work of breathing, these muscles can quickly fatigue and the infant can go into rapid respiratory arrest.²¹

Bradycardia is also a finding to pay close attention to in a child. The normal resting heart rate for an infant is higher than for an older child and adult. As well, normal infant compensatory measures can produce reflex tachycardia in response, which can easily be misinterpreted. However, with bradycardia, the infant and toddler are at a much higher risk of respiratory failure and/or bradycardic arrest.²² Also, inferences can be made about an infant's circulatory volume from assessment of peripheral capillary refill and skin tone appearance. Capillary refill in an infant should be brisk, <2–3 seconds, which can be assessed by lightly blanching the skin at the top of the infant's big toe or on the heel. Delayed refill is a sign that there is shunting of peripheral blood distribution due to a disruption in vascular tone. Skin mottling, often normally present in a cold infant to some degree, is also a finding that can signify vascular tone disruptions as well.²³

... KNOW WHEN TO FOLD 'EM

It is highly recommended to use clear, well-understood, prespecified stopping criteria for any OFC, but, in particular, stopping criteria is an important feature for OFCs in infants. Stopping criteria has been a key feature of all published clinical trials that involved OFCs in infants and has been highlighted as a key safety feature, potentially responsible for the low rates of anaphylaxis in those trials.^{3–7,13} The recently published AAAAI workgroup report¹³ details proposed stopping criteria in the context of an infant peanut OFC for early peanut introduction, which can be generalized to any infant challenge (Table 3). These stopping criteria provide organ-specific signs and/or symptoms that reasonably constitute when an objective reaction is occurring and when the OFC should be stopped and the infant treated. Other criteria have been published as well.^{13,16} With whichever criteria are used, including

Table 3 Recommended potential OFC stopping criteria*

Organ System	Symptoms (stop for any single symptom present)
Skin	≥3 hives; angioedema; confluent erythematous or pruritic rash
Lungs	Wheezing; stridor; recurring cough; increased work of breathing; dyspnea; change in or loss of voice
Gastrointestinal	Vomiting; colic; inconsolability
Cardiovascular	Hypotension; loss of consciousness
Additional recommendations	Stop OFC if ≥2 of the following are present: ≥3 min of either skin scratching, nose and/or eye rubbing, or rhinorrhea; diarrhea

OFC = Oral food challenge.

*Adapted and modified from Ref. 13.

ones that an individual practice may adapt on their own, the assessing providers must be in agreement with the criteria and be able to identify these objective symptoms.

For providers less familiar with infants, there are several more-subtle infant behaviors that could indicate an evolving reaction, which highlights the potential difficulty in performing OFCs in infants and why many may be resistant to performing these in the routine outpatient setting. Providers should consider stopping the OFC for more subtle signs such as ear picking, tongue rubbing, putting a hand in the mouth, neck scratching, behavioral changes (e.g., the infant becomes clingy, fussy, or acts more withdrawn).¹⁸ Although most reported data from the clinical trials that involved OFCs in infants indicate a high likelihood that the initial reaction in these infants is likely to be cutaneous only, anaphylaxis can occur and can occur without skin involvement.

TREATING ANAPHYLAXIS IN AN INFANT IS NOT DISTINCT FROM TREATING ANAPHYLAXIS IN ANY OTHER AGE!

Anaphylaxis treatment principles do not differ by age, only the medication doses differ, as discussed earlier. Dosing for epinephrine is 0.1–0.15 mg, administered intramuscularly, and this can be given every 5–10 minutes as with any other age group.^{17,19} If epinephrine is given, then positioning of the infant is essential. The infant needs to be held with the thigh (vastus lateralis muscle) isolated for the intramuscular injection, and, as with other ages, the infant should remain in the recumbent position for ease of cardiac blood flow, which minimizes the risk of empty ventricle syndrome (Simons et al.,¹⁸ Figure 1). As noted earlier, bradycardia is a very ominous and often late sign. Specific pediatric advanced lifesaving protocols are available for critical bradycardia, which include instructions for how and/or where to apply chest compressions and what medications to administer.²⁴ Infants are at risk for both warm and cold shock. Assessing providers must be observant of skin color and/or

capillary refill changes, which can be subtle clues to the infant's circulatory status. Hypotension is often a very late finding. If shock is suspected, then early fluid support is indicated by using the aforementioned volume of 10-mL/kg boluses to prevent edema.^{22,23}

AFTERCARE

Once OFC is complete, families must be advised on how to feed the child. There are no evidence-based targets for how much an infant must have in his or her diet on a daily or weekly basis.²⁵ Although the National Institutes of Allergy and Infectious Diseases (NIAID) addendum guidelines¹¹ recommend a target dose of 2 g, three times per week of peanut, this is a recommended target and was based on what happened to be used with success in the Learning Early About Peanut Allergy (LEAP) trial⁴ (with similar targets for peanut and other foods used in the as well). However, it is of note that LEAP/Enquiring About Tolerance (EAT)⁵ dosing targets were not tested for efficacy, EAT study, that said, they did work and are not unreasonable amounts, but other dosing quantities and frequencies may also work.^{4,5} The general advice that should be given to parents is to aim for regular frequency in the diet and an age-appropriate serving size, similar to how other foods were introduced. It is advised to discuss in advance what the post-OFC feeding plan and goals are or to have the parents start considering these.¹³ How much allergen needs to be ingested after the challenge to promote tolerance is an ongoing area of research that likely will evolve over time. On discharge, even though this ingestion was tolerated, parents should be counseled on signs and/or symptoms of a reaction because it is possible (though rare) that the child may react on a subsequent ingestion a few days later.

If OFC failed (e.g., the infant reacts and does not tolerate the food), then the infant should be managed as per established food allergy management guidelines for patients of any age.¹ The infant needs to be prescribed self-injectable epinephrine; be provided a written anaphylaxis management plan (and have that plan

Table 4 Summary of key findings of studies that involve infant OFCs

Study/Reference	Methodology	Intervention	Rate of Anaphylaxis	Comments
Health Nuts/ Osborne <i>et al.</i> ³	Prospective trial, OFC conducted to sesame, egg, peanut in 1500 children ages 12–18 mo	Assessment of prevalence of food allergy proven by OFC	14 Reactions with observed cardiac or respiratory symptoms	Urticaria was the most common presenting symptom in OFCs with reactions
Bellach <i>et al.</i> ⁸	Prospective, randomized controlled trial of raw egg in n-406 infants not at risk	Early introduction of raw egg at 4 mo, all enrolled infants had egg sIgE < 0.35 KU/L	10/16 Infants sensitized to egg developed anaphylaxis on initial raw egg exposure.	This group with anaphylaxis was screened and had sIgE of >0.35 KU/L, and were excluded from the trial but still challenged
Palmer <i>et al.</i> ⁹	Prospective, randomized controlled trial of raw egg in n-86 infants at risk	Early introduction of raw egg at 4 mo, all participants had moderate-to-severe eczema	10/15 reacted on initial raw egg exposure but only 1 case of anaphylaxis	Study terminated early because a third of the participants had a reaction to the raw egg
Wei-Liang <i>et al.</i> ⁶	Double blind, randomized controlled trial of n-319 infants at risk	Early introduction of raw egg at 4 mo, all infants with a first-degree relative with a history of atopy and the infant had a negative egg skin test result	None	14 Mild reactions were noted
Palmer <i>et al.</i> ⁷	Double blind, randomized controlled trial of n-820 infants at risk	Early introduction of raw egg at 4 mo; all the infants without any atopy but with a mother with atopy	2/28 had anaphylaxis on initial introduction	Mostly mild reactions
Natsume <i>et al.</i> ¹⁰	Double blind, randomized controlled trial of n-121 infants at risk	Early introduction of small amount of cooked egg from 6–9 mo, then a larger amount from 9–12 mo; all the infants had moderate-severe atopic dermatitis	None	9 Infants had minor symptoms during the first 10 days vs 11 events in the placebo group
Du Toit <i>et al.</i> ⁴	Randomized controlled trial of n-640 infants at risk	Early introduction of peanut between 4 and 11 mo vs deliberately delayed introduction until 60 mo in children with either egg allergy and/or moderate-to-severe eczema	None	7 Baseline reactions in the 4–11-mo olds, none required epinephrine
Perkin <i>et al.</i> ⁵	Randomized controlled trial in n-1303 infants not at risk	Early, sequential introduction of peanut, milk, cooked egg, sesame, fish, wheat in exclusively breast-fed infants but not atopic at either 3 mo of life or after 6 mo of life	None	7 Reactions that did not require epinephrine in the entry challenge reactions

OFC = Oral food challenge.

explained to them verbally); be counseled on strict avoidance and aftercare issues, such as label reading and cross-contamination; and discuss specific measures and care if the infant is in childcare.¹⁸ It is also important to schedule regular follow-up care for ongoing testing and/or evaluation. There is favorable natural history for milk, egg, wheat, and soy allergy, and up to 25% may outgrow peanut allergy by age 4 years.^{1,26} Thus, it is important to help parents maintain a healthy perspective that all hope is not lost, and that, despite having the allergy diagnosed this early in life, the child may outgrow the allergy or that treatment may be available. There are no data with regard to whether a quality-of-life deficit may develop from a very early diagnosis; this represents a potentially evolving area of research.

WHAT IS THE PRACTICAL EXPERIENCE?

There are multiple recent studies that demonstrate the safety and efficacy of OFCs in children ages ≤ 18 months, to better emphasize that this is a safe procedure. These studies include ample data in children <12 months of life to further emphasize that OFCs in this age range are not only feasible but also safe.^{3,5} The majority of data are limited to peanut and raw egg challenges, but there is also evidence for cooked egg, fish, sesame, wheat, and milk. However, these data are all from outside the United States and limited to large randomized controlled trials, which may or may not represent a generalizable situation to one's office. Most reactions that have been noted are mild and cutaneous. Although anaphylaxis has also occurred, no cases have required intensive care unit admission, and most of the data from the trials indicate that epinephrine was not needed apart from the few severe reactions.³⁻⁵ The main findings from some of these trials with respect to reaction severity are detailed in Table 4.

SUMMARY OF KEY CONSIDERATIONS

OFCs in infants are a safe and invaluable service to provide. As with any OFC in other ages, preparation is essential. Before attempting OFC in an infant, one should have a clear indication for the procedure, obtain parental written consent before starting, and ensure that these are performed only in a properly monitored setting (which could be one's office). It is essential to have a dedicated room and supervision for the OFC, and to plan this to occur at a time when the child does not typically nap. Having accurate weight and vital signs, having appropriate weight-based doses of emergency medications readily on hand, and having familiarity with age-appropriate vital signs are crucial. It is highly recommended to use pre-established stopping criteria and have a pre-

specified treatment plan, including transfer contingency to the nearest emergency department if necessary. For the vehicle, have age appropriate doses and/or vehicles and multiple options available in case of poor cooperation, and there should be clear discharge instructions provided to the parents in the event of either a passed or failed challenge. Remember. Overall experience has been that these are safe. Good luck!

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