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Updating the CoFAR Grading Scale for Systemic Allergic Reactions in Food Allergy

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Abstract

Background: Immunotherapy is promising as an efficacious treatment for food allergy. Other food allergy treatments are also under development. However, adverse allergic events (AE)

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during treatment, as well as during oral food challenges (OFC) are common and reporting is not standardized.

Objective: A more nuanced grading scale is needed to create a comprehensive and universal system to categorize AEs and their severity for food allergy clinical trials.

Methods: Starting with the 2012 Consortium for Food Allergy Research (CoFAR) Grading Scale and the World Allergy Organization (WAO) Grading System, we developed the CoFAR Grading Scale for Systemic Allergic Reactions, Version 3.0, in collaboration with industry partners with expert opinion.

Results: The revised CoFAR Grading Scale for Systemic Allergic Reactions has five levels of increasing severity, ranging from generalized urticaria, localized angioedema, rhinitis, and abdominal pain (Grade 1) to death (Grade 5). Systemic reactions are further categorized within each grade by relevant organ system. Mild, single-system reactions are differentiated from mild, multi-system reactions. Lower respiratory symptoms are graded based on response to therapy; those that are refractory to standard treatment (e.g., requiring >3 doses of IM epinephrine, continuous IV epinephrine infusion, continuous albuterol nebulization) and respiratory compromise requiring mechanical ventilation are classified as Grade 4, life-threatening reactions.

Conclusion: Universal and consistent use of the revised CoFAR Grading Scale beyond the CoFAR centers would allow for better data aggregation and safety comparisons in clinical trials for food allergy.

CAPSULE SUMMARY:

- The updated CoFAR Grading Scale provides more granular tracking of not only the grade of reactions, but the organ systems involved and the response to treatment, allowing for safety comparisons between studies.

Keywords

Food allergy; grading; anaphylaxis; severity scale; CoFAR; oral food challenge; oral immunotherapy

Introduction

IgE-mediated food allergy is estimated to affect 8% of children and 10.8% of adults in the United States and causes substantial morbidity for those with the disease.[1] Consequently, research on the prevention and treatment of food allergy has increased and is starting to yield potential treatment options. In 2020, Peanut (*Arachis hypogaea*) allergen powder-dnfp (formerly AR101) was approved by the FDA and European Commission for oral immunotherapy.[2] Other promising therapies for a variety of foods are under active clinical investigation in Phase 1 to Phase 3 trials, with a multitude of delivery routes (e.g., oral, sublingual, epicutaneous, injectable)[3,4] and novel treatment strategies (e.g., anti-IgE [5–13], anti-IL-33[14], anti- IL-4Rα antibodies; synthetic peptides; DNA-LAMP vaccines[3]; and others) are being evaluated.[3] As more trials are undertaken, it is important to have a comprehensive and universal system to categorize adverse events (AEs) and their severity,

in order to support consistent data collection and facilitate comparisons of risks and benefits among treatment options.[15] There are a few groups working to establish standardized grading systems for food allergy. Dribin et al have proposed a new grading system that incorporates anaphylactic and non-anaphylactic reactions; this system classifies reactions on a 5-point scale that does not include death[16]. The DeFASe project (Consensus project on the Definition of Food Allergy Severity) is currently employing Delphi methodology to better identify a scoring system that not only incorporates symptom severity, including anaphylactic and non-anaphylactic reactions, but also incorporates impact on quality of life and health economics.[17]

The Consortium for Food Allergy Research (CoFAR) had previously developed the CoFAR Grading Scale for Allergic Reactions to address AEs associated with procedures specific to food allergy studies, such as oral food challenges (OFCs) and oral immunotherapy dosing (Table 1).[18] Since its publication in 2012, this grading scale has been adopted for use in multiple trials.[18–20] However, the general descriptions of the five grading categories that were established to reflect the wide range of symptoms that may be experienced, allowed for significant investigator discretion. More recently, the U.S. Food and Drug Administration (FDA) and the CoFAR investigators determined that it was too subjective for wide-scale use. A grading system that incorporates objective signs and symptoms that may occur in food-induced allergic reactions, similar to the modified World Allergy Organization (WAO) Grading System for Severe Allergic Reactions for aeroallergen immunotherapy, became necessary.

Results and Discussion

The advantage of the revised CoFAR Grading Scale (CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0) is its coverage of the full spectrum of potential allergic reactions, including cutaneous, conjunctival, gastrointestinal (GI), upper and lower respiratory tract, and cardiovascular symptoms, enabling consistent and standardized classification and reporting of reactions associated with OFCs and food allergen immunotherapy. It is applicable to all patient populations including children and adults undergoing OFCs or food allergen immunotherapy to any food. Importantly, it categorizes systemic allergic reactions, not local reactions, and defines the criteria required for reactions involving only 1 organ system to be a systemic reaction (e.g., generalized urticaria alone is a Grade 1 systemic allergic reaction). It also differentiates mild, single-system reactions from mild multi-system reactions (e.g. mild conjunctival injection is a Grade 1 reaction while the combination of mild conjunctival injection and mild nausea is a Grade 2 reaction). This revised CoFAR Grading Scale differs from the modified WAO Grading System in that it has been designed specifically for food allergic reactions. Reactions to subcutaneous immunotherapy commonly involve local cutaneous reactions which is germane given the method of allergen delivery. However, with allergen ingestion, as in food allergy, AEs involving the GI tract are more common and not necessarily reflective of a more severe reaction.[21] Thus, mild abdominal pain is designated Grade 1 in the CoFAR Grading Scale, as opposed to Grade 3 in the modified WAO Grading System. Furthermore, GI symptoms resulting in a change in the level of activity, a common occurrence in food allergy assessments, are now identified as a discriminating factor between a Grade 1 and

Grade 2 GI symptom. Importantly, any symptom listed under the organ system description could qualify for grading and the severity of the symptom will guide which grade is appropriate. For instance, while GI symptoms often occur together (nausea, abdominal pain, and vomiting), only one symptom from the category is needed to potentially be a qualifying symptom. Abdominal pain alone could be dose limiting and graded based on the investigator's determination of the severity.

In the revised CoFAR Grading Scale, Grade 3 AEs include lower respiratory symptoms that are readily responsive to short-acting bronchodilator treatment such as 1–2 doses of intramuscular (IM) epinephrine and/or albuterol. Grade 4 reactions are similar to the original 2012 grading scale and meant to capture life-threatening reactions that require higher level medical intervention, such as lower respiratory symptoms that are refractory to standard treatment (e.g., more than 3 doses of IM epinephrine, continuous IV epinephrine infusion, continuous albuterol nebulization) or respiratory compromise requiring mechanical ventilation. Additionally, Grade 4 reactions include reduced blood pressure with corresponding clinical manifestations. Grade 5, death, is unchanged in Version 3.0. Although exceedingly rare, fatalities have occurred during OFCs[22] and need to be captured in a safety reporting system. Grade 5 has been used to classify fatal events in most commonly used AE grading scales for other conditions, such as the Common Terminology Criteria for Adverse Events (CTCAE).[23]

In addition to the revised CoFAR Grading Scale, CoFAR has also developed guidance for the interpretation of OFCs performed in food allergy studies. OFCs are the primary measure of efficacy endpoints in food allergy clinical trials. Furthermore, by virtue of how OFCs are conducted, a single additional dose during an OFC can significantly alter the interpretation of the results and ultimately the assessment of efficacy of the treatment. When conducting OFCs, the decision as to when the challenge is considered positive and should be halted is open to vast inconsistency across clinical trials. Therefore, in addition to the revised CoFAR Grading Scale, CoFAR is now providing clearer descriptions of dose-limiting symptoms during OFCs in an effort to standardize the definition of a positive OFC and provide guidance on when to stop an OFC (Table 3). While most of the symptoms listed in this table are captured within the new grading scale, there are some notable exceptions. Neurological symptoms were not included in the grading scale; instead, more objective criteria for the underlying pathology, i.e., hypotension, were set forth. Additionally, cutaneous symptoms are listed in each of the mild, moderate, and severe columns in Table 3, however, there can be significant investigator discretion in the attribution of severity between moderate and severe symptoms. Thus, moderate and severe cutaneous symptoms listed in Table 3 are considered moderate symptoms for the organ system on the CoFAR Grading Scale and are captured as Grade 2.

The reporting of anaphylaxis throughout an allergy clinical trial may be mandated by regulatory agencies. An explicit definition of anaphylaxis is not presented in either table as several different published definitions exist and are used by various organizations (WAO, EAACI, AAAAI/ACAAI, ASCIA, and NIAID).[16,17,24,25] One could reference any of these specific anaphylaxis grading systems to provide a clear definition for the use of the term. However, given that anaphylaxis simply reflects a more severe systemic allergic reaction,

investigators could use the proposed CoFAR Grading Scale categories to determine whether the reaction in question meets existing definitions of anaphylaxis presented elsewhere to avoid redundancies. None of the previous or current scales address anaphylaxis within the grading system. Table 4 highlights key elements of each of the scales.

We recognize potential limitations with use of this or any other grading scale. In fact, no grading scale, including the widely used grading scale previously developed by CoFAR, has been validated. Validation would be difficult without a gold standard for comparison but future research could be designed to formally compare two or even three existing scales. In summary, while any protocol can choose to use whatever grading scale best fits its needs, we believe that our scale does provide unique advantages. Universal and consistent use of the revised CoFAR Grading Scale beyond the CoFAR centers could allow for better data aggregation and safety comparisons across many different settings and treatment protocols. This updated grading scale improves upon prior versions with more granular tracking of not only the grade of reactions, but the organ systems involved and the response to treatment. If used widely in a systematic fashion, it will allow for meaningful comparisons of the risks and benefits of novel treatments for food allergies. Paired with mechanistic investigations, we can begin to endotype the food allergic individual based on their AE phenotype, not only at the time of food challenges, but throughout the course of treatment, bringing us closer to precision medicine in food allergy.

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ABBREVIATIONS

FDA	Food and Drug Administration
AAAAI	American Academy of Allergy, Asthma & Immunology
ACAAI	American College of Allergy, Asthma, and Immunology
AE	Adverse events
ASCIA	Australasian Society of Clinical Immunology and Allergy
CoFAR	Consortium for food allergy research
CTCAE	Common Terminology Criteria for Adverse Events
EAACI	European Academy of Allergy and Clinical Immunology
IM	Intramuscular
NIAID	National Institute of Allergy and Infectious Diseases
OFC	Oral food challenges
WAO	World Allergy Organization

REFERENCES

1. Sicherer SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food Allergy from Infancy Through Adulthood. J Allergy Clin Immunol Pract. 2020;8(6):1854–1864. [PubMed: 32499034]
2. fda.gov [Internet]. U.S. Food & Drug Administration; c2020 [cited 2020 Oct 12]. Available from: https://www.fda.gov/vaccines-blood-biologics/allergenics/.
3. Sampath V, Sindher SB, Alvarez Pinzon AM, Nadeau KC. Can food allergy be cured? What are the future prospects? Allergy. 2020;75(6):1316–1326. [PubMed: 31733120]

4. Chinthrajah RS, Purington N, Andorf S, Long A, O'Laughlin KL, Lyu SC, et al. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. Lancet. 2019;394(10207):1437–1449. [PubMed: 31522849]
5. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol. 2017;139(3):873–881.e878. [PubMed: 27609658]
6. Andorf S, Purington N, Block WM, Long AJ, Tupa D, Brittain E, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. Lancet Gastroenterol Hepatol. 2018;3(2):85–94. [PubMed: 29242014]
7. Andorf S, Purington N, Kumar D, Long A, O'Laughlin KL, Sicherer S, et al. A Phase 2 Randomized Controlled Multisite Study Using Omalizumab-facilitated Rapid Desensitization to Test Continued vs Discontinued Dosing in Multifood Allergic Individuals. EClinicalMedicine. 2019;7:27–38. [PubMed: 31193674]
8. Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med. 2003;348(11):986–993. [PubMed: 12637608]
9. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol. 2011;127(6):1622–1624. [PubMed: 21546071]
10. Savage JH, Courneya JP, Sterba PM, Macglashan DW, Saini SS, Wood RA. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. J Allergy Clin Immunol. 2012;130(5):1123–1129.e1122. [PubMed: 22800401]
11. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol. 2013;132(6):1368–1374. [PubMed: 24176117]
12. Bégin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. Allergy Asthma Clin Immunol. 2014;10(1):7. [PubMed: 24576338]
13. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol. 2016;137(4):1103–1110.e1111. [PubMed: 26581915]
14. Chinthrajah S, Cao S, Liu C, Lyu SC, Sindher SB, Long A, et al. Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. JCI Insight. 2019;4(22).
15. Muraro A, Fernandez-Rivas M, Beyer K, Cardona V, Clark A, Eller E, et al. The urgent need for a harmonized severity scoring system for acute allergic reactions. Allergy. 2018;73(9):1792–1800. [PubMed: 29331045]
16. Dribin TE, Schnadower D, Spergel JM, Campbell RL, Shaker M, Neuman MI, et al. Severity grading system for acute allergic reactions: A multidisciplinary Delphi study. J Allergy Clin Immunol. 2021.
17. Arasi S, Nurmatov U, Dunn-Galvin A, Daher S, Roberts G, Turner PJ, et al. Consensus on DEfinition of Food Allergy SEverity (DEFASE) an integrated mixed methods systematic review. World Allergy Organ J. 2021;14(3):100503. [PubMed: 33767801]
18. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233–243. [PubMed: 22808958]
19. Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol. 2017;139(4):1242–1252 e1249. [PubMed: 28091362]
20. Palisade Group of Clinical Investigators, Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, et al. AR101 Oral Immunotherapy for Peanut Allergy. N Engl J Med. 2018;379(21):1991–2001. [PubMed: 30449234]
21. Stafford A, Patel N, Turner PJ. Anaphylaxis-moving beyond severity. J Allergy Clin Immunol. 2021;148(1):83–85. [PubMed: 33901514]

22. Pouessel G, Beaudouin E, Tanno LK, Drouet M, Deschildre A, Labreuche J, et al. Food-related anaphylaxis fatalities: Analysis of the Allergy Vigilance Network((R)) database. Allergy. 2019;74(6):1193–1196. [PubMed: 30636053]

23. ctep.cancer.gov [Internet]. U.S. Departmet of health and human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. 2017; c2017 [cited 2020 Oct 12]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

24. Turner PJ, Worm M, Ansotegui IJ, El-Gamal Y, Rivas MF, Fineman S, et al. Time to revisit the definition and clinical criteria for anaphylaxis? World Allergy Organ J. 2019;12(10):100066. [PubMed: 31719946]

25. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006;47(4):373–380. [PubMed: 16546624]

CLINICAL IMPLICATIONS

- Food-induced systemic allergic reaction grading scales for adverse event reporting during food allergy and immunotherapy studies are not standardized and a refined grading scale is needed to harmonize safety reporting across food allergy.
- The revised CoFAR Grading Scale incorporates objective signs and symptoms that may occur in food-induced allergic reactions.
- Universal and consistent use of the CoFAR Grading Scale will allow for better data aggregation and safety comparisons across many different settings and treatment protocols.

Table 1

Update of the Food-Induced Systemic Allergic Reaction Grading Scale by the Consortium for Food Allergy Research

Prior CoFAR Grading Scale for Allergic Reactions[18]				
Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**	**Grade 5 Death**
Transient or mild discomforts (<48 hours), no or minimal medical intervention/therapy required. These symptoms may include pruritus, swelling or rash, abdominal discomfort or other transient symptoms.	Symptoms that produce mild to moderate limitations in activity some assistance may be needed; no or minimal intervention/therapy is required. Hospitalization is possible. These symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort / increased vomiting of other symptoms	Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization is possible. Symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, transient hypotension among others. Parenteral medication(s) are usually indicated.	Extreme limitation in activity, significant assistance required; significant medical/ therapy. Intervention is required; hospitalization is probable. Symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse or other life-threatening symptoms.	Death

Table 2

CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Reaction involving **one of the following organ systems in which the symptoms are mild**: Cutaneous Generalized pruritus, generalized urticaria, flushing, angioedema Upper respiratory Rhinitis, cough unrelated to laryngeal edema or bronchospasm Conjunctival Injection/redness, itching, tearing GI Nausea, abdominal pain (no change in activity level), single episode of vomiting and/or single episode of diarrhea	Reaction involving **two or more of the following organ systems in which the symptoms are mild**: Cutaneous Generalized pruritus, generalized urticaria, flushing, angioedema Upper respiratory Rhinitis, cough unrelated to laryngeal edema or bronchospasm Conjunctival Injection/redness, itching, tearing GI Nausea, abdominal pain (no change in activity level), single episode of vomiting, and/or single episode of diarrhea **OR** Reaction involving **at least one of the following organ systems in which the symptoms are moderate:** Cutaneous[1] Generalized pruritus, generalized urticaria, flushing, angioedema Upper respiratory Rhinitis, cough unrelated to laryngeal edema or bronchospasm Conjunctival Injection/redness, itching, tearing GI Nausea, abdominal pain (with change in activity level), two episodes of vomiting and/or diarrhea	Reaction involving **one or more of the following organ systems**: Lower respiratory Throat tightness, wheezing, chest tightness, dyspnea, cough that respond to short-acting bronchodilator treatment (including IM epinephrine) with or without supplemental oxygen GI Severe abdominal pain, more than two episodes of vomiting and/or diarrhea	**Life-threatening reaction** involving **one or more of the following organ systems** with or without other symptoms listed in Grades 1 to 3: Lower respiratory Throat tightness with stridor, wheezing, chest tightness, dyspnea, or cough associated with a requirement for supplemental oxygen and refractoriness[2] to short-acting bronchodilator treatment (including IM epinephrine) **OR** Respiratory compromise requiring mechanical support Cardiovascular Reduced BP with associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope) defined as: • Children: low systolic BP (age specific[3]) or >30% decrease in systolic BP • Adults: systolic BP of less than 90 mmHg or >30% decrease from baseline	Death

[1] Moderate or severe cutaneous symptoms are captured as Grade 2.

[2] Examples of refractoriness could include continuous albuterol nebulizer or epinephrine IV infusion or more than three IM epinephrine injections.

[3] Low systolic BP for children is defined as: less than 70 mmHg from 1 month to 1 year of age, less than (70 mmHg + [2 × age]) from 1 to 10 years of age, and less than 90 mmHg from 11 to 17 years of age.

Table 3:

Definition of Dose-Limiting Symptoms

Mild (not typically dose limiting)	Moderate (dose limiting)	Severe (dose limiting)
• Skin – limited (few) or localized hives, swelling (e.g., mild lip edema), skin flushing (e.g., few areas of faint erythema) or mild pruritus (e.g., occasional scratching) • Respiratory – rhinorrhea (e.g., occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort • GI – mild abdominal discomfort (including mild nausea with or without decreased activity), isolated emesis thought to be secondary to gag	• Skin – systemic hives (e.g., numerous or widespread hives), swelling (e.g., significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema • Respiratory – throat tightness without hoarseness, persistent cough, wheezing without dyspnea • GI – persistent moderate abdominal pain/cramping/ nausea with decreased activity, vomiting	• Skin – severe generalized urticaria/ angioedema/erythema • Respiratory – laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor • GI – severe abdominal pain/cramping/repetitive vomiting • Neurological – change in mental status • Circulatory – clinically significant hypotension

Oral food challenges (OFCs) will be considered positive with the occurrence of any dose-limiting symptoms during a single dose, which in the view of the PI indicate a true allergic reaction which should preclude the administration of any further doses. As defined in the table, mild symptoms are not usually considered dose-limiting, although a combination of mild symptoms during a single dose might lead to the cessation of an OFC at the discretion of the PI. All moderate and severe symptoms as defined in the table are considered dose-limiting.

Table 4:

Similarities and major differences between available grading scales

Prior CoFAR	Current CoFAR (V3)	WAO 2017[22]	Dribin et al[16]
• Specifically designed for food-induced allergic reactions • Grades determined mainly by limitation in activity and intervention required • Limited examples of signs/ symptoms given for each grade, but not comprehensive • Great deal of investigator discretion allowed in determining severity	• Specifically designed for food-induced allergic reactions • Grades broken down by number and type of organ system(s) involved, as well as severity of symptoms • Signs/ symptoms for each grade provided in far more detail than in CoFAR V1 • Investigator discretion in assigning grade minimized	• Update of WAO 2010 grading system • Designed for reactions due to all triggers, but primarily utilized for subcutaneous immunotherapy • Similar to CoFAR V3 with a few major differences (e.g. isolated abdominal cramps or vomiting Grade 3 in WAO but Grade 1 in CoFAR V3 until there are changes in activity level)	• Very specific grading scale, broken down by number and type of organ system(s), as well as symptom severity • Includes detailed subgrading system based on clinical criteria • Designed for generalizability (e.g in the emergency department, rather than specifically for food-induced reactions