

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



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Background: Immunotherapy is promising as an efficacious treatment for food allergy. Other food allergy treatments are also under development. However, adverse allergic events during treatment, as well as during oral food challenges, are common and reporting is not standardized.

Objective: A more nuanced grading scale is needed to create a comprehensive and universal system to categorize adverse events 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 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 5 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, multisystem reactions. Lower respiratory tract symptoms are graded on the basis of response to therapy; those that are refractory to standard treatment (eg, requiring >3 doses of intramuscular epinephrine, continuous intravenous epinephrine infusion, and continuous albuterol nebulization) and respiratory compromise requiring mechanical ventilation are classified as grade 4, life-threatening reactions.

Conclusions: 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. (*J Allergy Clin Immunol* 2022;149:2166-70.)

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This work was supported by the National Institutes of Health (grant nos. SUM1AI130839 and SUM2AI130836).

Disclosure of potential conflict of interest: R. S. Chinthrajah receives grant support from the Consortium for Food Allergy Research (CoFAR), the National Institute of Allergy and Infectious Diseases (NIAID), Food Allergy Research & Education (FARE), Aimmune, DBV Technologies, Astellas, Novartis, and Regeneron, and is an advisory board member for Alladapt Immunotherapeutics, Novartis, Sanofi, and Genentech. S. M. Jones reports grants to her institution from the NIAID and from FARE; clinical trials funding to her institution from Aimmune Therapeutics, Inc, DBV Technologies, Inc, Regeneron Pharmaceuticals, Inc, Astellas Pharma, Inc, and Genentech, Inc; and personal fees from Aimmune Therapeutics, Inc, as a member of the Scientific Advisory Board and Food and Drug Administration advisory consultant, from Regeneron Pharmaceuticals, Inc, as a research advisory consultant, and from Astellas Pharma, Inc, as scientific advisory consultant. E. H. Kim reports medical advisory board membership with DBV Technologies, Kenota Health, and Ukko, Inc; consultancy with Aimmune Therapeutics, DBV Technologies, Duke Clinical Research Institute, ALK, AllerGenis, Nutricia, Jubilant Hollister-Stier, Belhaven Biopharma, HAL Allergy, and Allergy Therapeutics; and receives grant support to his institution from the National Institutes of Health (NIH)/NIAID, the National Center for Complementary and Integrative Health (NIH/NCCIH), FARE, and the Wallace

Research Foundation. S. H. Sicherer reports royalty payments from UpToDate and from Johns Hopkins University Press; grants to his institution from the NIAID, from FARE, and from HAL Allergy; and personal fees from the American Academy of Allergy, Asthma & Immunology as Deputy Editor of *the Journal of Allergy and Clinical Immunology: In Practice*, outside of the submitted work. W. Shreffler reports grants to his institution from the NIAID and from FARE; clinical trials funding to his institution from Aimmune Therapeutics, Inc, DBV Technologies, Inc, Regeneron Pharmaceuticals, Inc, Astellas Pharma, Inc, and Genentech, Inc; and personal fees from Aimmune Therapeutics, Inc, as a member of the Scientific Advisory Board and from Regeneron Pharmaceuticals, Inc, Sanofi, and Novartis as a scientific advisory consultant. B. J. Lanser reports grants and personal fees from Aimmune Therapeutics, DBV Technologies, and Genentech; grants from Regeneron; personal fees from Allergis, Hycor, and GlaxoSmithKline; and grant support to his institution from the NIH/NIAID. D. C. Adelman was employed by Aimmune Therapeutics, Inc, and receives personal fees from Aimmune Therapeutics, Inc, as a member of the Scientific Advisory Board, and from IgGenix, Inc, as a research advisor. A. Iqbal is employed by Genentech. S. L. Limb was employed by Genentech. R. A. Wood reports grants from the US NIH, Astellas, Aimmune, DBV Technologies, Genentech, Sanofi, and Regeneron, and personal fees from UpToDate. The rest of the authors declare that they have no relevant conflicts of interest. A. K. R. Spergel, N. Atri, and A. Togias' coauthorship of this publication does not necessarily constitute endorsement by the NIAID, the NIH, or any other agency of the US government.

Received for publication September 3, 2021; revised December 28, 2021; accepted for publication December 30, 2021.

Available online January 11, 2022.

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0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2021.12.789>

Key words: 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 Food and Drug Administration and the European Commission for oral immunotherapy.² Other promising therapies for various foods are under active clinical investigation in phase 1 to phase 3 trials, with a multitude of delivery routes (eg, oral, sublingual, epicutaneous, and injectable)^{3,4} and novel treatment strategies (eg, anti-IgE,⁵⁻¹³ anti-IL-33,¹⁴ anti-IL-4R α antibodies; synthetic peptides; DNA-LAMP vaccines³; 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, 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 al¹⁶ have proposed a new grading system that incorporates anaphylactic and nonanaphylactic reactions; this system classifies reactions on a 5-point scale that does not include death. The DeFASe project (Consensus project on the Definition of Food Allergy Severity) is currently using Delphi methodology to better identify a scoring system that incorporates not only symptom severity, including anaphylactic and nonanaphylactic reactions, but also 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 I).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 5 grading categories that were established to reflect the wide range of symptoms that may be experienced allowed for significant investigator discretion. More recently, the US Food and Drug Administration 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; Table II) 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

Abbreviations used

AE: Adverse event
CoFAR: Consortium for Food Allergy Research
GI: Gastrointestinal
OFC: Oral food challenge
WAO: World Allergy Organization

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 (eg, generalized urticaria alone is a grade 1 systemic allergic reaction). It also differentiates mild single-system reactions from mild multisystem reactions (eg, mild conjunctival injection is a grade 1 reaction, whereas 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, although GI symptoms often occur together (nausea, abdominal pain, and vomiting), only 1 symptom from the category is needed to potentially be a qualifying symptom. Abdominal pain alone could be dose limiting and graded on the basis of investigator's determination of the severity.

In the revised CoFAR Grading Scale, grade 3 AEs include lower respiratory tract symptoms that are readily responsive to short-acting bronchodilator treatment such as 1 to 2 doses of intramuscular epinephrine and/or albuterol. Grade 4 reactions are similar to those in the original 2012 grading scale and meant to capture life-threatening reactions that require higher-level medical intervention, such as lower respiratory tract symptoms that are refractory to standard treatment (eg, more than 3 doses of intramuscular epinephrine, continuous intravenous epinephrine infusion, and continuous albuterol nebulization) or respiratory compromise requiring mechanical ventilation. In addition, 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 OFCs²² 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.²³

In addition to the revised CoFAR Grading Scale, CoFAR has developed guidance for the interpretation of OFCs performed in food allergy studies. OFCs are the primary measure of efficacy end points in food allergy clinical trials. Furthermore, by virtue of

TABLE I. Update of the food-induced systemic allergic reaction grading scale by CoFAR

Previous 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 h), 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 and 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, or 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) is 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 II. CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0

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

BP, Blood pressure; IM, intramuscular; IV, intravenous.

*Examples of refractoriness could include continuous albuterol nebulizer or epinephrine IV infusion or >3 IM epinephrine injections.

†Low systolic BP for children is defined as <70 mm Hg from 1 mo to 1 y, <(70 mm Hg + [2 × age]) from 1 to 10 y, and <90 mm Hg from 11 to 17 y.

‡Moderate or severe cutaneous symptoms are captured as grade 2.

TABLE III. Definition of dose-limiting symptoms

Mild (not typically dose limiting)	Moderate (dose limiting)	Severe (dose limiting)
● Skin—limited (few) or localized hives, swelling (eg, mild lip edema), skin flushing (eg, few areas of faint erythema) or mild pruritus (eg, occasional scratching) ● Respiratory—rhinorrhea (eg, occasional sniffing 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 (eg, numerous or widespread hives), swelling (eg, 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

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 that 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.
PI, Principal investigator.

TABLE IV. Similarities and major differences between available grading scales

Previous 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 used for subcutaneous immunotherapy ● Similar to CoFAR V3 with a few major differences (eg, 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 (eg, in the emergency department, rather than specifically for food-induced reactions)

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 III). Although 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, that is, hypotension, were set forth. In addition, cutaneous symptoms are listed in each of the mild, moderate, and severe columns in Table III; 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 III 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 because several different published definitions exist and are used by various organizations (WAO, European Academy of Allergy and Clinical Immunology, American Academy of Allergy, Asthma &

Immunology/American College of Allergy, Asthma, and Immunology, Australasian Society of Clinical Immunology and Allergy, and National Institute of Allergy and Infectious Diseases).^{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 IV 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 criterion standard for comparison, but future research could be designed to formally compare 2 or even 3 existing scales.

In summary, although 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 previous versions with more granular tracking of not only the grade of reactions but also 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 on the basis of 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.

We thank the CoFAR-10 investigators and collaborators Adrian Dana, MD, Kari Brown, MD, and Anoshie Ratnayake, MD (from Aimmune), and CoFAR-11 investigators Jonathan Spergel, MD, PhD, Brian Vickery, MD, and Drew Bird, MD, for their valuable input.

Clinical implications

- Food-induced systemic allergic reaction grading scales for AE 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.

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METHODS

Using the previous CoFAR grading system and the modified WAO Grading System^{E1} as a guide, the new CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0 (Table II) was developed. The revised grading system was developed by the CoFAR Steering Committee, composed of representatives from the 7 CoFAR clinical sites, in collaboration with experts from the National Institute of Allergy and Infectious Diseases, the CoFAR Coordinating Center (Rho, Inc), and industry partners.^{E2} The first iteration (V1.0) was implemented across 9 sites for a phase 3 clinical trial in September 2020.

Adjustments were made to clarify reactions that are considered life-threatening, and Version 3.0 has been in use since March 2021.

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