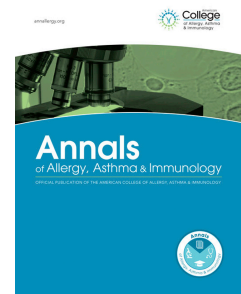


Journal Pre-proof

What constitutes a severe food allergy reaction?

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PII: S1081-1206(20)30390-2

DOI: <https://doi.org/10.1016/j.anai.2020.05.027>

Reference: ANAI 3264

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 1 April 2020

Revised Date: 7 May 2020

Accepted Date: 25 May 2020

Please cite this article as: Spergel ZC, Kennedy K, Alfaro MKC, Dorris SL, Capucilli P, What constitutes a severe food allergy reaction?, *Annals of Allergy, Asthma and Immunology* (2020), doi: <https://doi.org/10.1016/j.anai.2020.05.027>.

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Title: What constitutes a severe food allergy reaction?

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Author commentary: All authors above met full authorship criteria including the following: (1) made substantial contributions to conception and design, acquisition of data, and/or analysis and interpretation of the data; (2) drafted the article or reviewed it critically for important intellectual content; (3) gave final approval of the version to be published; (4) agree to be accountable for all aspects of the work related to its accuracy or integrity.

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Key words: Anaphylaxis, Severe reaction, Epinephrine, PRACTALL, COFAR

Conflicts of Interest: None

Funding: None

Clinical trial registration: None

Word Count:998

Figures: 0 Tables: 1

1 IgE-mediated food allergy (FA) accounts for the leading cause of anaphylaxis in children,
2 though fatal reactions remain rare.^{1,2,3} Strict adherence to avoidance diets and use of FA
3 emergency management plans can decrease reaction rates significantly, with one study
4 demonstrating a 60-fold reduced frequency of severe FA reactions.⁴ However, which patients
5 experience severe vs mild symptoms, as well as contributory factors, remains an area of active
6 study.^{5,6} Currently, no unified definition of a severe FA reaction exists, calling into question
7 which symptom or compilation of symptoms during a reaction constitute a severe label.

8 A common scale used to grade elicited reactions during physician-observed oral food
9 challenges (OFC), is the PRACTALL double blind placebo-controlled food challenge
10 (DBPCFC) scale,⁷ though several other scales have been utilized both in research and clinical
11 settings.^{8,9} Comprehensively, cardiovascular, neurologic, lower respiratory and laryngeal
12 symptoms, or presence of multiple-system reactions are consistently graded among the highest
13 severity categories across scales. However, based on variations between tools, individual crude
14 scores may not be complementary, limiting comparison across institutions and providers. This
15 confines our understanding of severity of FA reactions on a global level and how severity may
16 change over time. Based on our use of the PRACTALL scale in clinical practice and the CoFAR
17 Anaphylaxis Severity Score grading system in recent clinical trials,⁸ we sought to better
18 understand correlation between these tools and how grading outcomes further correlate with
19 clinical markers.

20 We performed a retrospective chart review of all patients who underwent OFC at the
21 Children's Hospital of Philadelphia (CHOP) and Vanderbilt University Medical Center (VUMC)
22 between 9/9/16 and 2/28/19. Data was extracted from both institutions' electronic medical
23 records (EMR) (Epic Systems, Verona, WI) and compiled for statistical analysis. An honest

broker removed direct patient identifiers to create a dataset inclusive of patient demographics, atopic history, and OFC outcomes. At CHOP, all OFCs were performed in a hospital-based medicine unit, while OFCs at VUMC were performed in the outpatient clinic setting with both institutions following challenge protocols outlined in the PRACTALL guidelines.⁷ Outcomes for positive (reacted) challenges at CHOP were graded using the PRACTALL score at time of reaction and were entered into the EMR by a dedicated allergy nurse involved in the food challenge. All PRACTALL scores for OFC at VUMC were retrospectively scored by an attending allergist. All reactions at both institutions were then retrospectively scored using the CoFAR Anaphylaxis Severity Score⁸ based on chart review by two attending allergists with any discrepancies differentiated by a third allergist.

Graded challenges were evaluated for severity based on five different criteria including: (1) total PRACTALL score, (2) presence of lower respiratory, laryngeal, cardiovascular or neurologic sub-scores using the PRACTALL scale, (3) number of epinephrine doses administered during reaction, (4) total CoFAR score, and (5) number of organ systems involved during reaction. Cardiovascular/neurologic involvement included hypotension, cardiovascular collapse, change in mental status or loss of consciousness. Laryngeal/lower respiratory symptoms included hypoxia, bronchospasm, throat tightness, stridor or respiratory failure, which along with individual organ systems, were outlined based on the PRACTALL scale.⁷ Linear regression analysis was used for comparison between criteria. Data were analyzed using GraphPad v.8 (Prism Software, San Diego, Calif). The study was approved by each individual site's Institution Review Board.

A total of 744 OFCs with a positive clinical reaction were reviewed (CHOP n=677, VUMC n=67). There were 459 male and 218 female subjects, with mean age of 6.91 years,

ranging from 0.5 to 18.7 years. Multiple OFCs were completed in 49 subjects (4 patients- 4 challenges, 6 patients- 3 challenges, 39 patients- 2 challenges). Total PRACTALL scores ranged from 1 to 24 (mean: 5.08 ± 3.17). Epinephrine doses ranged from 0-4 (1 patient had 4 doses, 6 patients- 3 doses, 62 patients-2 doses and 371 -1 dose) Correlations between the 5 measures ranged by best linear fit: (r^2 from 0.01 to 0.50) with highest correlation between total PRACTALL score and number of organ system involved (0.50) and number of epinephrine doses and total PRACTALL score (0.36) (Table 1).

In this study we compared different measures of FA reaction severity to better understand correlation between clinical markers and scores on two individual reaction grading scales. The highest correlations were noted between total PRACTALL score and number of organ systems involved in the reaction, as well as PRACTALL score and number of epinephrine doses received (Table 1). However, globally, our results suggest that different measures of severity do not correlate well with each other. Importantly, correlation between total composite scores on our two selected scales, PRACTALL and CoFAR, was poor ($r^2=0.31$). These results are similar to previous studies and editorials delineating inconsistencies in reaction severity classification.^{9,10}

Strengths of our study include a large pediatric population and reaction classification determined directly at the time of food challenge, limiting possible patient/parent recall bias. All reaction scores at CHOP were entered prospectively by dedicated OFC allergy nurses familiar with classification using the PRACTALL score, which strengthens the internal integrity of our data. Limitations of our study include use of different graders between institutions and retrospective grading of challenges for the VUMC cohort, however, proportionally, this accounted for a smaller overall percentage. In addition, it is important to note that OFCs were not

double blinded, and onset of reaction may have led to early treatment of reactions potentially limiting the overall severity with variance based on attending clinician at time of OFC.

In conclusion these data suggest the need for a standardized scoring system for anaphylaxis. Future efforts should assess physician use of anaphylaxis grading scales across institution and potential work group efforts to standardize clinically relevant allergic reaction scoring. Physicians caring for patients with FA should be able to objectively identify which patients have exhibited a severe reaction as this will help guide patient education, long-term monitoring, as well as potential treatment, including immunotherapy qualifications. Such data may also be useful as advancements in our field seek to better understand potential biomarkers that contribute to individual patient reaction severity, and the mechanisms that underlie disease development and proliferation.

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	EPINEPHRINE DOSE	COFAR SCORE	TOTAL PRACTALL SCORE	# OF ORGAN SYSTEM	CARDIO/LOWER RESP/NEURO*
EPINEPHRINE DOSE	X	0.285	0.352	0.228	0.190
COFAR SCORE	0.285	X	0.310	0.388	0.403
TOTAL PRACTALL SCORE	0.352	0.310	X	0.519	0.267
# OF ORGAN SYSTEM	0.228	0.388	0.519	X	0.334
CARDIO/LOWER RESP/NEURO*	0.190	0.403	0.267	0.334	X

Table 1: Correlations between the 5 measures of food reaction severity studied, demonstrated by goodness of Fit- R^2 . Abbreviation: Neuro, neurologic; * indicates presence of cardiovascular, lower respiratory/laryngeal or neurologic sub-scores using the PRACTALL scale.