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anaphylaxis, epinephrine, children, food-induced, grading system, severity,

Abbreviations used:

CNS: Central nervous system

CRD: Component-resolved diagnostics

FIA: Food-induced anaphylaxis

LTP: Lipid transfer proteins

OFC: Oral food challenge

SAR: Systemic allergic reactions

sIgE: Specific immunoglobulin E

Abstract

Background:Significant discrepancies among anaphylaxis severity scores may delay epinephrine administration.

Objective:The study aims to develop a transparent severity grading system of food-induced acute allergic reactions with decision model for epinephrine use.

Methods:The natural course of 315 acute food-induced allergic reactions in children hospitalized at the Allergology Department between May 2016, and July 2019 due to follow-up treatment and/or allergy diagnostics, was evaluated. The severity of episodes was classified according to the five most accepted grading systems. The inter-rater reliability of classification between anaphylaxis severity scores was assessed. All

symptoms were grouped into a heat map according to their real-life incidence and clinical relevance. Based on the heat map analysis, a severity grading system of food-induced acute allergic reactions in children, with the epinephrine administration decision model, was created.

Results: Data from 259 food-induced anaphylaxis episodes in 157 children were included in the analysis. Comparing the grading systems, we observed from 24.7% to 70.2% disagreement between severity scores. The heat map showed a strong association between 29 symptoms and their categorization. A new severity grading system was developed and a two-stage decision model was proposed: “epinephrine yes” (any rapidly progressing symptoms, even mild or from one organ system; any symptoms from more than one organ system; every grade of anaphylaxis), and “epinephrine available and prepared to use” (non-progressing mild systemic allergic reaction from one system area only; no anaphylaxis).

Conclusion: A new severity grading system of food-induced acute allergic reactions in children could serve as a clinical tool for healthcare professionals to avoid epinephrine administration delay.

Introduction

Food-induced anaphylaxis (FIA) is the most frequent type of anaphylaxis and the most common cause of fatal allergic reactions in children.¹⁻⁵ FIA may lead to death after accidental consumption at large,² extremely rarely during controlled oral food challenge (OFC),² or even after accidental cutaneous contact.⁶ At the same time, epinephrine is underused during FIA presenting a risk of fatal and near-fatal anaphylaxis.³ Because the clinical course of anaphylaxis is unpredictable, epinephrine should be administered promptly as soon as anaphylaxis is suspected.⁷⁻¹⁷

On the other hand, some real-life food-induced acute allergic reactions are mild^{4,18,19}; most of them are self-limiting and resolve without evolving into anaphylaxis.¹⁸ These mild reactions do not require immediate epinephrine administration, as demonstrated by clinical experience and as highlighted in guidelines and care plans.^{9,13,18,20} Diagnostic criteria of anaphylaxis are not ideal for identifying patients who should be treated with epinephrine.²¹ Moreover, numerous anaphylaxis guidelines and care plans differ significantly.^{13-17,20,22} Thus, the primary assistance that guides the treatment is the symptoms severity score.^{23,24}

Several systems have been developed to quantify anaphylaxis severity. None is ideal, and none is validated.²⁵ They vary considerably, mainly due to a lack of homogenous settings, different age cohorts,^{26,27} and different triggers, e.g., food,²⁷⁻²⁹ drugs,³⁰ venom,³¹ or allergen

immunotherapy.³²⁻³⁴ Some are based on expert opinion,^{26,28,32,33,35-37} very few on real-life anaphylaxis.^{31,38} They use different definitions of anaphylaxis, cover only the essential symptoms,^{26,30,31} or a broad spectrum of symptoms.^{28,33} Transpositions of significant symptoms between grades often exist.^{28,30,31,33} Hence, the new severity score is long-awaited by healthcare practitioners.³⁵

To date, severity scores for FIA have been developed, totally or partially, based on clinically controlled OFC.^{2,23,29} However, OFC differs from the real-life FIA picture and may not consider the reaction in its entirety.^{33,39,40} It has been shown that challenge is usually stopped after the first, often mild signs.^{24,35,39-41} Real-life anaphylaxis, on the other hand, often depends on total dosage, which may be large or small. Even a small bite could potentially trigger a full anaphylactic reaction. Therefore, the severity score validated by the natural course of real-life FIA is needed.

Based on the natural history of food-induced acute allergic reactions in a large pediatric population, this study aimed to put the principles of anaphylaxis definition, severity grades, and the care plans together in one system with a treatment decision model that could be useful in a daily practice of healthcare providers to simplify the decision-making and avoid the delay of epinephrine administration.

Methods

Study Design, Population, and Definitions

The study was conducted between May 2, 2016, and July 4, 2019 at Allergology and Pulmonology Department, National Research Institute for Tuberculosis and Lung Diseases - Rabka-Zdroj, Poland. All subjects and their parents/caregivers were informed of the purpose of the study and provided written informed consent. The study was approved by the Institutional Review Board.

Children with food-induced acute allergic reactions admitted to the pediatric Emergency Department and subsequently hospitalized at the Allergy Department due to follow-up treatment and/or detailed allergy diagnostics were prospectively included. The diagnosis of systemic allergic reaction (SAR) or anaphylaxis and its severity according to specified severity grading system was always made by the same anaphylaxis expert (LB), based on the same survey and upon an in-depth analysis of medical history, clinical symptoms closely correlated with the ingested food, and analysis of the available medical records.

Food-induced anaphylaxis definition was based on the criteria published by the Australasian Society of Clinical Immunology and Allergy¹⁰ and the World Allergy Organization Anaphylaxis Committee.¹¹

Food-induced anaphylaxis

Anaphylaxis was defined as (i) acute onset illness developing after exposure to food allergen with skin or mucosal symptoms (e.g., generalized urticaria, flushing, pruritus, angioedema) and involvement of respiratory (e.g., dyspnea, bronchospasm, upper airway obstruction) or cardiovascular (e.g., hypotension, end-organ dysfunction symptoms) or severe gastrointestinal symptoms (e.g., repetitive vomiting, crampy abdominal pain) or (ii) any acute onset of relevant hypotension or bronchospasm or upper airway obstruction (laryngeal involvement) after exposure to a food allergen, even if typical skin features are not present.

Relevant hypotension was defined as a decrease in systolic blood pressure (B.P.): (i) in children 0-10 years less than $(70 \text{ mmHg} + [2 \times \text{age in years}])$; (ii) in children over 10 years less than 90 mmHg.⁸ Laryngeal involvement includes stridor, vocal changes, or odynophagia.¹¹

Systemic allergic reaction

Mild, non-life-endangering and non-progressing symptoms from one organ system only, limited to the skin/mucosal tissue (generalized urticaria, pruritus, flushing or angioedema,

except for upper airway angioedema), or the gastrointestinal tract (tingling mouth/oral pruritus, nausea), or the upper airway (nasal/eye symptoms, throat pruritus) were classified as systemic allergic reaction.³³

If there was no association of the acute allergic reaction with food ingestion, such a reaction was not included in the study.

Data Collection

Medical history was assessed and blood samples were collected. Medical records were supplemented in detail by the parents or caregivers in the clinic and independently reviewed and abstracted by two investigators, including one anaphylaxis expert (LB). The investigators collected relevant information on demographics, individual reaction features (symptoms and signs, including the order in which the symptoms appear), culprit triggers (ingested food up to 4 hours before first signs of anaphylaxis), anaphylaxis cofactors, treatment and outcomes of the episode using a standardized case report form for data collection. All data were entered by the staff directly into the database.

Allergy profile evaluation and measurement

Skin prick tests using standardized extracts of food and inhalant allergens were performed, according to standard guidelines⁴², with histamine 10 mg/ml as a positive control. If skin prick tests and sIgE did not confirm the trigger, prick-to-prick tests with fresh food were performed following guidelines.⁴² Moreover, serum samples were taken from all patients to confirm the specific immunoglobulin E (sIgE) of anaphylaxis trigger at the allergen component level. Serum-specific IgE (sIgE) was measured using two assays (multiplex ImmunoCAP ISAC[®]112 and singleplex ImmunoCAP[®]100; ThermoFisher Scientific) according to the manufacturer's instruction, as was previously described⁴³. The ImmunoCAP ISAC microarray immunoassay measures sIgE to 112 allergen components, including 43 food allergen components. The results were expressed in ISU-E (ISU-E: ISAC Standardized Units,

standardized to ImmunoCAP sIgE units), and sensitization was defined as a sIgE concentration ≥ 0.3 ISU-E. ImmunoCAP[®]100 was used to measure sIgE to hazelnut allergen Cor a 14 and cashew nut allergen Ana o 3, which are not included in ImmunoCAP ISAC. A positive result was defined as 0.35 kUA/L or more.

Severity Grading System Analysis and Study Outcomes

The Muraro³⁶ scale was used for classifying the severity of FIA symptoms. This is a three-stage scale, developed in 2007, and is the first grading system based on a consensus definition of anaphylaxis developed in 2006.⁸

Next, anaphylaxis severity was classified according to the four widely accepted severity grading systems listed below.

(i) Mueller HL,³¹ a four-stage scale, was published in 1966, based on reactions to insect stings in over 300 children. This classification formed the basis for what has followed since then. The scale was modified by Mueller UR in 1990.⁴⁴

(ii) Ring,³⁰ a four-stage scale, was established in 1999 (final version) using a prototype that was published in 1977 based on 69 acute reactions to infusion of colloid volume.

(iii) Sampson,²⁸ a five-stage scale, was developed in 2003 based on expert opinion to standardize

double-blind, placebo-controlled food challenges with the term "anaphylaxis" referring to all the symptoms resulting from an IgE-mediated response to a food allergen.

(iv) Cox,³³ a five-stage scale, was formed in 2017 based on expert opinion as a modification of the WAO 2010 score for allergic reactions due to allergen immunotherapy.

Data analysis

Due to the high heterogeneity and significant discrepancies among the baseline anaphylaxis severity scores at the individual symptom level (Figure 1), we adjusted five-stage

scales (Sampson, Cox) to four-stage scores before statistical analysis of these disagreements. The adaptation process is described and visualized in e-Methods, eFigure 1 and eFigure 2.

After adaptation, Fleiss' kappa measure was used to assess the percentage of disagreement of anaphylaxis severity classification according to four-stages scales (Mueller, Ring, adapted Sampson, and adapted Cox) based on symptoms from 259 food-induced anaphylaxis episodes in the study population. Next, we grouped all the symptoms of anaphylaxis in our pediatric population into a four-stage heat map according to their real-life incidence and clinical relevance in the natural history of anaphylaxis. According to the heat map results and based on the clinical picture and treatment decisions made during the 259 analyzed events, a new visual severity grading system of acute food-induced allergic reactions in children and decision model for epinephrine administration were created as clinical tools for healthcare professionals.

Comparisons of severity grading systems were made using Cohen's kappa coefficient to measure inter-rater reliability for categorical items. For a similar measure of disagreement, Fleiss' kappa was used to compare all four severity scores.

Results

Baseline characteristics

A total of 315 cases of food-induced acute allergic reactions in 210 Caucasian children aged 0-18 years were analyzed. Fifty-six reactions did not meet the criteria for anaphylaxis and were excluded due to mild and non-progressing symptoms from one organ system classified as systemic allergic reactions. Finally, we analyzed 259 real-life food-induced anaphylaxis episodes in 157 children. Demographics and baseline clinical characteristics of the study population and anaphylaxis events are shown in Table 1. Out of 157 children, 103 (56.6%) were boys. Most children (56.1%) had one reaction, while 12.7% had three or more FIA

episodes. In the three-stage Muraro scale, 23.6% of reactions were severe. Skin/mucosal symptoms were the most frequent (81.1%), followed by respiratory signs (58.3%).

The triggers of food-induced anaphylaxis in each severity grade, at the level of allergen extract, allergen family, and allergen component, are shown in Figure 2.

Allergen extract

In each severity grade, cow's milk was the most frequent trigger, while hen's egg was the trigger mainly in grades 1 and 2. Peanut allergy was the cause of anaphylaxis with almost the same frequency in each severity grade. The most frequent causes of grade 3 anaphylaxis were cow's milk, peanuts, and cashew nuts (26%, 11%, and 7%, respectively).

Allergen family

Storage proteins from nuts, legumes, wheat, and seeds were the most frequent FIA triggers in severity grade 1 and 2, while caseins, storage proteins, and lipid transfer proteins were the most frequent triggers in grade 3 (26%, 25%, and 15%, respectively).

Allergen components

Bos d 8 (casein, milk), Ara h 2 (2S albumin, peanut), Gal d 1 (ovomucoid, egg), Ana o 3 (2S albumin, cashew nut), and Jug r 1 (2S albumin, walnut) were the most frequent triggers of severe (grade 3) food-induced anaphylaxis in the study population (26%, 10%, 7%, 7%, and 3%, respectively).

Grading system comparison

After the classification of all the symptoms from 259 episodes according to four-stage scales (Mueller, Ring, adapted Sampson, and adapted Cox), we observed 24.7% (Mueller vs. Cox) to 70.2% (Mueller vs. Ring) disagreement among severity scores. According to Landis and Koch's interpretation of Cohen's kappa, we found from slight to moderate inter-rater agreement (Table 2). After including all the scores, Fleiss' kappa reached 0.4, which is the upper bound for fair inter-rater agreement.

Creation of a new grading system

We grouped all 29 symptoms (Table 3) of FIA in a four-stage heat map according to their clinical relevance and real-life incidence in the study population (Figure 3). The heat map showed strong associations between symptoms and their categorization. Based on the heat map analysis, clinical picture, and treatment of 259 events, a visual severity grading system of food-induced acute allergic reactions was created. Six columns contain symptoms from six systems involved in anaphylaxis: skin, gastrointestinal (G.I.), upper respiratory, lower respiratory, cardiovascular, and central nervous system (CNS). The symptoms are arranged in several grades depending on their clinical severity, starting with mild systemic allergic reactions to four grades of anaphylaxis (Figure 4). The most severe symptom determines the severity grade.

According to the proposed score, the prevalence of anaphylaxis symptoms in the study population in particular severity grades are shown in Table 4 and Figure 3. Angioedema was the most frequent skin symptom and was observed in 52% of reactions in all severity grades (63%, 44%, 53%, and 58% in grades 1, 2, 3, and 4, respectively). Among G.I. symptoms, repetitive vomiting was the most frequent (28% of FIA) and occurred in 46%, 24%, and 50% in grades 2, 3, and 4, respectively. Almost one-third (31%) of reactions with isolated G.I. symptoms and no skin signs at the onset progressed to anaphylaxis with respiratory and/or cardiovascular compromise. Upper airway angioedema was the most frequent (10% of FIA) upper respiratory symptom and occurred in 31% and 16% of grade 3 and 4, respectively. Upper airways were involved in 55,6% of grade 3 and 4 reactions. Among lower respiratory symptoms, bronchospasm was predominant (26% of FIA) and led to respiratory failure in 16% of grade 4 reactions. CNS symptoms were present in 13% of FIA, and 50% preceded severe cardiovascular symptoms, resulting in 83.3% of grade 4 reactions.

Epinephrine administration was the highest in grade 4 (58.3%) (Table 4).

Epinephrine administration decision model

The decision model to administer epinephrine is presented in two stages. Stage 1 – "*epinephrine yes.*" This stage includes (i) rapidly progressing symptoms (within minutes), even mild or from one organ system; (ii) any symptoms from more than one system area; and (iii) every grade (I-IV) of anaphylaxis. Stage 2 – "*epinephrine available and prepared to use.*" This stage is limited to mild and non-progressing systemic allergic reactions from one system area only (skin or mouth or nose/eyes) and no anaphylaxis.

Discussion

To our knowledge, this is the first study established to create the severity grading system of food-induced acute allergic reactions based on the natural history of real-life cases in a pediatric population. We grouped all the symptoms of 259 food-induced anaphylaxis episodes into a four-stage heat map based on their incidence and clinical relevance. After this clinical validation, we proposed a new visual severity grading system with two-stage epinephrine decision points.

Due to non-homogenous settings (e.g., different age cohorts and triggers) and the use of different anaphylaxis definitions, considerable inconsistency among anaphylaxis grading systems exists.^{25,35} We have shown relevant differences among most used anaphylaxis severity scores based on real-life FIA symptoms in our pediatric population. Transpositions of significant cardiovascular or respiratory symptoms, e.g., hypotension, bronchospasm, or upper airway angioedema, between grades often exist. Many significant symptoms are missing, e.g., confusion, somnolence, collapse, pale and floppy, repetitive cough. This is in line with Ruiz Oropeza et al., who showed that using one score, up to 28% of the anaphylaxis cases could not be graded in another score due to the absence of some symptoms⁴⁵. Therefore, a new severity score organized according to the prevalence and significance of all real-life

anaphylaxis symptoms is needed and expected by practitioners.³⁵ In Figure 1, we present our proposal by comparing it to previously described severity scores.

Symptoms and severity grades.

Several groups of experts have proposed the criteria for the ideal severity grading system.^{25,35,37} First, it should be applicable for all anaphylaxis triggers, e.g., venom, food, and drugs. However, different symptoms have different clinical relevance in various triggers and exposure routes due to anaphylaxis heterogeneity. Urticaria, labial angioedema, tingling in the mouth, oral pruritus, or nausea during food-induced acute allergic reaction are in most cases not rapidly progressive, mild, and the only symptoms. In contrast, in anaphylaxis due to drug injection or insect sting, the above symptoms may be the first signs of a life-threatening reaction, even if they do not occur immediately.^{37,46} Therefore, a uniform system for each trigger may lead to incorrect severity assessment. Our study was established to create a score exclusively for FIA. This is in line with the principles of personalized medicine.⁴⁷

Second, the ideal score should be simple and useful in the daily practice.^{25,35,37} We propose a four-stage grading system that includes 29 symptoms from the main six systems involved in anaphylaxis: skin, gastrointestinal, upper respiratory, lower respiratory, CNS, and cardiovascular.⁴⁸ The transparent division into six columns (systems) and four 'traffic' lights colors rows (severity grades) indicates the actual state of patient risk and reflects anaphylaxis as a continuum from mild to severe reactions.

Table 3 and Figure 4 present the prevalence of anaphylaxis symptoms in particular grades according to the proposed score. In 18.9% of cases, skin symptoms were absent, which is in line with the findings of others.^{3,8,26} Gastrointestinal signs can herald a severe anaphylactic reaction.^{26,31,36} In the present study, 31.0% of events with isolated gastrointestinal symptoms and no skin features at the onset progressed to reactions with respiratory and/or cardiovascular compromise.

The majority of fatal FIA is associated with respiratory failure.^{9,26,49} However, there are many discrepancies in the classification of severity of upper or lower airway symptoms.^{25,28,30-31,33,35-36} To increase transparency in a risk assessment, we split a broad spectrum of respiratory symptoms into the upper and lower airway. It stresses the importance of upper airway angioedema, which should alert clinicians towards severe and life-threatening reactions.^{33,36} In the study population, upper airways were involved in 55.6% of grade 3 and 4 reactions.

Some authors omit CNS symptoms, e.g., anxiety, weakness, or dizziness,^{30,33-34,50} or reject them as subjective.³⁷ However, if the onset of CNS signs is closely related to food exposure, most experts highlight their relevance as the first signs of end-organ dysfunction, which indicate reduced brain perfusion and correlate with hypotension, especially in infants.^{5,11,26,34,36} Eller et al. showed that in 70% of analyzed challenges, CNS symptoms were connected with objective signs of other systems.³⁵ In our population, CNS signs always followed the symptoms from other organ systems and 50.0% preceded cardiovascular compromise, which are considered life-threatening (grade 4).⁵¹ Cardiovascular symptoms occurred in 83.3% of reactions in grade 4, and the prevalence of these signs is higher than in previously published data.⁵

Decision model as a clinical tool

It is challenging to put all the puzzles (principles of definition, severity grades, and the care plans) together in one system. From a healthcare professional perspective, anaphylaxis diagnostic criteria are not sufficient to undertake a treatment decision.^{21,52} Clear decision points should be established in an anaphylaxis care plan, but many differences exist.^{9,13,18,20,22} Some allow for observation and hold off on epinephrine injection until additional symptoms occur or more than one organ system is involved.²² On the contrary, in

'extreme reactivity' to the ingested food, epinephrine administration recommendations, even if there are no anaphylaxis symptoms, are provided.²⁰ However, in the case of an acute reaction, healthcare providers have to take rapid decisions, and they need clear criteria for the injection of epinephrine.⁵³

Some of the real-life food-induced acute allergic reactions are mild^{4,18,19} (e.g., urticaria, non-progressing lips edema, lips tingling, or oral pruritus). They usually occur in the absence of other symptoms, and most of them are self-limiting.¹⁸ If they are not progressing, these mild reactions do not require immediate epinephrine administration, as reflected in guidelines and care plans.^{9,13,20} Turner et al.¹⁸ provide several essential arguments that the concept of "very early" epinephrine injection, given immediately at the onset of any symptom, seems to be an over invasive medical advice. On the other hand, the course of food-induced acute allergic reaction is unpredictable.⁵⁴ Even mild symptoms such as oral itching or urticaria, when progressing rapidly in a few minutes, are very serious signs and may herald a life-threatening reaction needing immediate action and epinephrine administration. The lack of precise algorithms creates the possibility of treatment omission.

We propose an easy-to-use decision model as a clinical tool both to avoid epinephrine delay and to prevent epinephrine overtreatment. The strategy is presented in two practical stages clearly specifying when epinephrine is *necessary* (stage 1) and when epinephrine should be *prepared for possible use* (stage 2) depending on detailed clinical judgment in any given patient.

Stage 1 – "*epinephrine yes*"-- provides for epinephrine use in every grade (I-IV) of anaphylaxis, in rapidly progressing symptoms (within minutes and even when mild or from one organ system), and in cases involving more than one system area.^{9,13-15,20} Stage 2 – "*epinephrine available and prepared to use*" – provides for epinephrine preparation in cases of mild, non-progressing systemic allergic reaction from one system area only (skin or mouth

or nose/eyes). Moreover, in this stage, a lower threshold of epinephrine administration must be considered in the case of previous severe reactions or co-existent asthma or exposure to patient-relevant allergen. This is in line with the experts' recommendations.^{9,13,14,20,22}

Strengths and limitations

A significant strength of our study is that the proposed severity grading system is based on the incidence and clinical relevance of real-life food-induced acute allergic reaction symptoms in the pediatric population. Our patients' cohort was well-matched in terms of several elements: (i) it included only children; (ii) all the episodes were real-life anaphylaxis after food ingestion; (iii) there were no episodes due to oral food challenge or allergy diagnostic tests. The proposed score covers a broader spectrum than in other scales using 29 food-induced acute allergic symptoms and organizes them according to their clinical significance. Second, the visual grading system combines both definition, severity, and the care plan, which allows for a rapid assessment of actual patient risk and the necessity of treatment. We propose a transparent, two-stage decision model as a clinical tool to simplify the decision-making towards 'in time' epinephrine administration, "*epinephrine yes*" and "*epinephrine available and prepared to use*," based on detailed clinical judgment. Third, the system splits respiratory symptoms into the upper and lower airways to increase transparency in a risk assessment and emphasizes the importance of CNS symptoms as end-organ symptoms, prodromal to life-threatening reactions. Fourth, the system is intended only for food triggers because a uniform score for every trigger may be the reason for life-threatening, wrong severity assessment. Fifth, in all 157 children, we have done component resolved diagnostics (CRD) to diagnose anaphylaxis triggers at the allergen component level. CRD permits recognition of anaphylaxis triggers more precisely since (i) some allergen extracts do not contain relevant components or their amount is scarce, (ii) skin prick tests and sIgE to allergen extracts are confusing in the case of cross-reactivity between allergens, (iii) detection of some anaphylaxis triggers, e.g.,

lipid transfer proteins (LTPs) from peanut (Ara h 9), hazelnut (Cor a 8), peach (Pru p 3) or wheat (Tri a 14), as well as omega-5-gliadin (Tri a 19) from wheat is impossible without CRD.^{1,55,56}

The study has some limitations. First, our score was not validated in the different populations and range of settings and it is unknown whether our data could be replicated in another dataset. However, a large study population gives the basis for the clinical validation of a subjective score towards an objective score, as experts propose.²⁵ Second, all patients come from one clinical center and such a cohort could provide only a partial picture compared to population-based studies. Third, we did not perform OFC, which is the gold standard in food allergy diagnosis, but there are some concerns about OFC's safety and usefulness in confirming anaphylaxis trigger.^{24,36,40,57} Wainstein et al. showed that the eliciting dose itself did not predict anaphylaxis in one-fifth of children and there is no apparent relationship between dose and severity.⁵⁷ They concluded that OFC could not determine the outcome of anaphylaxis, and conversely, the history of anaphylaxis was not predictive of anaphylaxis on challenge. Fourth, we did not consider serum tryptase concentration since it is not a definitive marker of FIA in children,^{48,58} rarely (19.2%)⁵⁹ exceeds published thresholds, and tryptase level in the normal range does not rule out anaphylaxis.⁵⁸

Conclusions

Significant discrepancies among anaphylaxis severity grading systems and within care plans present risks of both delayed injection and overuse of epinephrine. The optimal severity grading system should be intuitive for use in clinical practice given that severity grades reflect a logical progression of disease severity as a continuum from mild to fatal.⁶⁰ The proposed visual severity grading system, based on the real incidence and clinical relevance of food-induced acute allergic reactions in the pediatric population, with a decision model as a clinical

tool for 'in time' epinephrine administration, could simplify decision-making by healthcare professionals. Further validation of our system in the population studies is indicated.

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Table 1. Baseline characteristics

Characteristics	N (%)
Children population, n	157
Median age (years) (SEM)	4.9 (0.3)
Gender, n (%)	
Male	103 (65.6)
Female	54 (34.4)
Anaphylaxis events, n	259
Number of anaphylaxis event/child, n (%)	
1	88 (56.1)
2	49 (31.2)
≥ 3	20 (12.7)
Anaphylaxis severity grades prevalence, Muraro scale ³⁶ , n (%)	
1	83 (32.0)
2	115 (44.4)
3	61 (23.6)
Anaphylaxis symptoms prevalence/severity grade, Muraro scale ³⁶	
Skin and mucosal, n (%)	210 (81.1)
Gastrointestinal, n (%)	102 (39.4)
Respiratory, n (%)	151 (58.3)
Neurological, n (%)	34 (13.1)
Cardiovascular, n (%)	37 (14.3)

Table 2. The comparisons of food-induced anaphylaxis severity classification according to different scores. Data are presented as a Cohen's *kappa* coefficient with 95% CI and weighted *kappa*. Inconsistence of classification (%) is given for all comparisons.

	inconsistent classification (%)	degree of agreement	Kappa	95%CI	Weighted Kappa
Meuller vs Ring	70,2	slight	-0.051	-0.121 to 0.019	0.16

Meuller vs Sampson	41,7	fair	0.382	0.313 to 0.451	0.541
Meuller vs Cox	24,7	moderate	0.585	0.507 to 0.662	0.701
Ring vs Sampson	31,2	moderate	0.411	0.323 to 0.500	0.616
Ring vs Cox	47,2	fair	0.282	0.211 to 0.353	0.481
Sampson vs Cox	29,8	moderate	0.551	0.480 to 0.621	0.687

Table 3. The list of signs and symptoms of food-induced anaphylaxis that were under investigation in the study population.

System	Signs and symptoms
Skin and mucosal	Pruritus, e.g., skin, lips tingling, lips itching, itchy eyes, itchy nose Flushing Generalized urticaria Angioedema (not laryngeal), e.g., swelling of lips, ears, eyes
Gastrointestinal	Oral/palatal pruritus, oral/palatal tingling Nausea/drooling Crampy abdominal pain Sudden and/or recurrent vomiting Diarrhea
Upper respiratory	Nasal symptoms, e.g., congestion, sneezing, rhinorrhea Throat pruritus Hoarseness Feeling of difficult breathing (no specific cause) Upper airway angioedema, e.g., tongue swelling, posterior pharyngeal edema (throat tightness), difficulty swallowing, odynophagia, difficulty talking

Lower respiratory	Stridor/"barky" cough
	Sudden, repetitive cough
	Chest tightness/dyspnea
	Mild to moderate bronchospasm
	Severe bronchospasm (not responding or worsening despite treatment)
	Respiratory failure
Neurological	Sudden change in behavior or activity level
	Presyncope (e.g., dizziness/weakness)
	Confusion/somnolence
	Feeling of impending doom
	Loss of consciousness (non-transient)
Cardiovascular	Sudden, relevant hypotension
	Pale & floppy child
	Short episode of collapse/syncope
	Cardiovascular failure/arrest
	Death

Table 4. Characteristics of anaphylaxis episodes and epinephrine administration in particular severity grades according to proposed score.

Characteristics	N (%)
Anaphylaxis events, n	259
Anaphylaxis severity grades prevalence, n (%)	
1	68 (26.3)
2	102 (39.4)
3	77 (29.7)
4	12 (4.6)
Anaphylaxis symptoms prevalence/severity grade	
Skin and mucosal, n (%)	210 (81.1)
Grade 1	65 (95.6)
Grade 2	74 (72.6)
Grade 3	60 (77.9)
Grade 4	11 (91.7)
Gastrointestinal, n (%)	102 (39.4)
Grade 1	4 (5.9)
Grade 2	60 (58.8)
Grade 3	30 (39.0)
Grade 4	8 (66.7)
Upper respiratory, n (%)	82 (31.7)

Grade 1	6 (8.8)
Grade 2	26 (25.5)
Grade 3	46 (59.7)
Grade 4	4 (33.3)
Lower respiratory, n (%)	96 (37.1)
Grade 2	57 (55.9)
Grade 3	34 (44.2)
Grade 4	5 (41.7)
Neurological, n (%)	34 (13.1)
Grade 2	9 (8.8)
Grade 3	19 (24.7)
Grade 4	6 (50)
Cardiovascular, n (%)	37 (14.3)
Grade 3	27 (35.1)
Grade 4	10 (83.3)
Death	0 (0)
Epinephrine administration, n (%)	27 (10.4)
Grade 1	1 (1.5)
Grade 2	1 (1.0)
Grade 3	18 (23.1)
Grade 4	7 (58.3)

A severity grading system of food-induced acute allergic reactions to avoid delay of epinephrine administration

Figure Legend

Figure 1

The major discordances among the most used anaphylaxis severity scores.

Figure 2

The prevalence (%) of triggers of 259 food-induced anaphylaxis in the study population at the level of allergen extract (A-C), allergen family (D-F), and allergen component (G-I).

Figure 3

The prevalence (%) of anaphylaxis symptoms in the study population according to the proposed severity grading system of food-induced acute allergic reactions. Data are presented as a heat map.

Figure 4

The severity grading system of food-induced acute allergic reactions with two-stage epinephrine decision model based on 259 real-life episodes in children.

eMethods

Due to heterogeneity and large discrepancy between the baseline anaphylaxis severity grading systems, before statistical analysis of these disagreements, we adapted the five-stage scales (Sampson, Cox) to the four-stage scores (eFigure 1 and eFigure 2). For this purpose, we removed the Sampson grade 1, which includes local symptoms not meeting the actual anaphylaxis criteria^{3,7,8}, and the remaining grades were lowered by one. Then, we removed Cox grade 2. This grade contains only mild systemic allergic reactions and replicates the symptoms of grade 1. Thus, Cox grades 3, 4, and 5 were lowered by one.

eFigure 1. Sampson HA (2003) adapted to four-stage severity grading system.

System & Sx	Skin	Gastro-intestinal	Upper respiratory	Lower respiratory	Neurological	Cardiovascular
Grade						
I	Generalized: • pruritus • flushing • urticaria • angioedema	• oral pruritus • oral tingling • mild lip swelling • nausea • emesis x's 1	• nasal congestion • sneezing		• change in activity level	
II		• repetitive vomiting	• rhinorrhoea • marked congestion • throat pruritus • throat tightness		• anxiety	• tachycardia increase > 15 bpm
III		• diarrhoea	• hoarseness • „barky” cough • difficulty swallowing	• dyspnoea • wheezing • cyanosis	• lightheadedness • feeling of impending doom	• dysrhythmia • mild hypotension
IV		• loss of bowel control		• respiratory arrest	• loss of consciousness	• severe bradycardia • severe hypotension • cardiac arrest

eFigure 2. Cox L (2017) adapted to four-stage severity grading system.

System & Sx Grade	Skin	Gastro-intestinal	Upper respiratory	Lower respiratory	Neurological	Cardiovascular
I	• urticaria • erythema • pruritus • angioedema • conjunctival symptoms	• tingling of lips • itching of lips • nausea • metallic taste	• sneezing • rhinorrhoea • nasal pruritus • nasal congestion • itchy throat	• cough not related to bronchospasm		
II		• abdominal cramps • vomiting • diarrhoea		• mild bronchospasm e.g. cough, wheezing, shortness of breath which responds to treatment		
III			• laryngeal edema with stridor	• severe bronchospasm not responding or worsening in spite of treatment		
IV				• respiratory failure	• loss of consciousness	• collapse • hypotension

Figure 1.

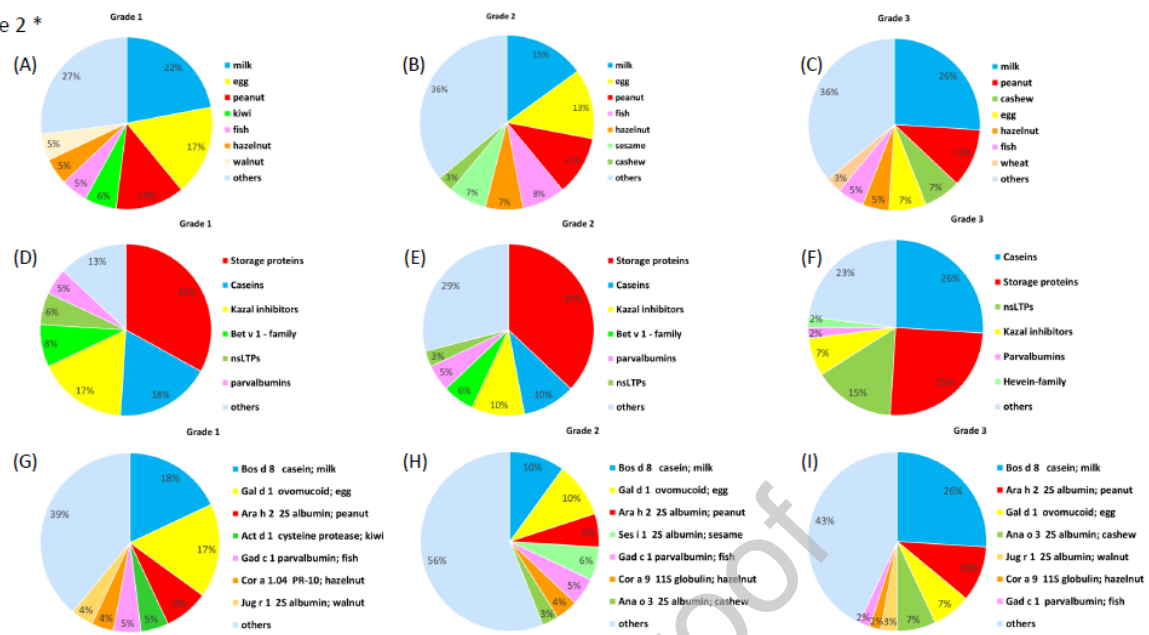
System	Symptoms	Mueller ³¹ 1966	Ring ³⁰ 1999	Sampson ²⁸ 2003 †	Muraro ³⁵ 2007	Cox ³³ 2017 †	Proposed grading system
Skin and mucosal	Pruritus e.g., skin, lips, eyes, nose	I	I	II	I	I	I
	Flushing	missing	I	II	I	I	I
	Generalized urticaria	I	I	II	I	I	I
	Angioedema (not laryngeal)	II	I	II	I	I	I
Gastrointestinal	Oral/palatal pruritus, oral/palatal tingling	missing	missing	I	I	I	I
	Nausea/drooling	II	II	II	I	I	I
	Crampy abdominal pain	II	II	missing	II	II	II
	Sudden and/or recurrent vomiting	II	III	III	II	II	II
	Diarrhea	missing	III	IV	II	II	II
Upper respiratory	Nasal symptoms	missing	II	II	I	I	I
	Throat pruritus	missing	missing	III	I	I	I
	Hoarseness	III	II	IV	II	missing	II
	Feeling of difficult breathing (no cause)	missing	missing	missing	missing	missing	II
	Upper airway angioedema*	III	III	IV	II	missing	III
	Stridor/barky cough	missing	missing	IV	II	IV	III
Lower respiratory	Sudden, repetitive cough	missing	missing	missing	missing	I	II
	Chest tightness/dyspnea	III	II	IV	II	III	II
	Mild to moderate bronchospasm	II	III	IV	II	III	II
	Severe bronchospasm**	III	III	IV	III	IV	III
	Respiratory failure	IV	IV	V	III	V	IV
Neurological	Sudden change in activity level	I	missing	II	I	missing	II
	Presyncope (dizziness/weakness)	II	missing	IV	II	missing	II
	Confusion/somnolence	III	missing	missing	III	missing	III
	Feeling of impending doom	III	missing	IV	II	missing	III
	Loss of consciousness (non-transient)	IV	III	V	III	V	IV
Cardiovascular	Sudden, relevant hypotension	IV	II	V	III	V	III
	Pale & floppy child	missing	missing	missing	missing	missing	III
	Short episode of collapse/syncope	IV	missing	missing	III	V	III
	Cardiac failure/arrest	IV	IV	V	III	V	IV

† Sampson 2003 and Cox 2017 scales are consist of five stages. The first stage involves mild systemic allergic reactions, and the fifth stage life-threatening symptoms.

* e.g., tongue swelling, posterior pharyngeal edema (throat tightness), difficulty swallowing, odynophagia, difficulty talking

** not responding or worsening despite treatment

Figure 2 *



* Anaphylaxis severity grades are presented according to Muraro³⁶ scale.
Abbreviations: nsLTPs, non-specific lipid transfer proteins

Figure 3

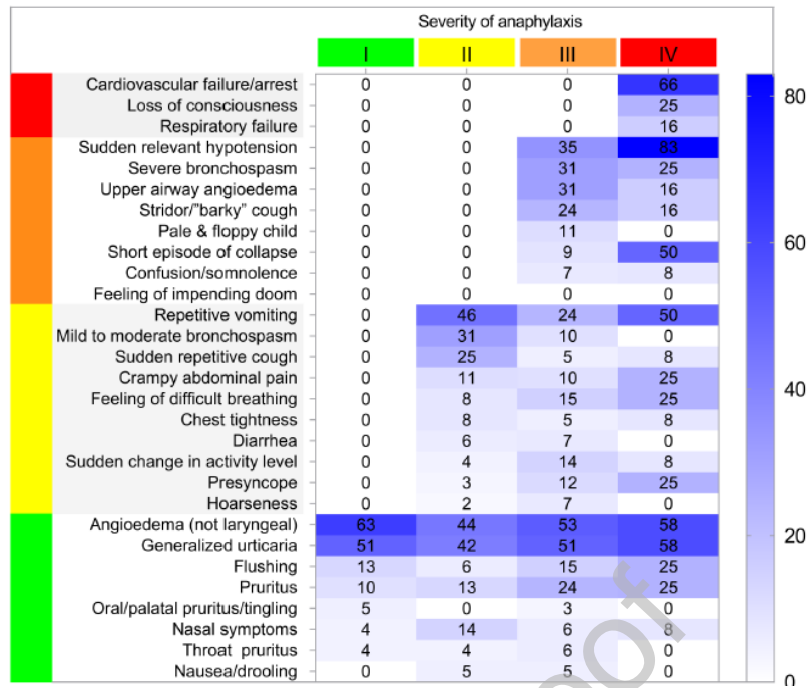


Figure 4

Figure 4

DETAILED CLINICAL JUDGMENT IS CRUCIAL FOR THE DECISION

EPINEPHRINE AVAILABLE*

EPINEPHRINE YES

IF NON-PROGRESSING Sx & ONLY 1 SYSTEM INVOLVED
PREPARE * EPINEPHRINE

IF RAPIDLY PROGRESSING Sx OR > 1 SYSTEM INVOLVED
GIVE EPINEPHRINE

GIVE EPINEPHRINE

GIVE EPINEPHRINE

GIVE EPINEPHRINE & RESUSCITATION

	SYSTEMS & Sx	SKIN/MUCOSAL	GASTRO-INTESTINAL	UPPER RESPIRATORY	LOWER RESPIRATORY	NEUROLOGICAL	CARDIOVASCULAR
GRADE †							
SYSTEMIC ALLERGIC REACTION		• urticaria • pruritus (e.g., skin, lips, eyes, nose) • flushing • angioedema (not laryngeal)	• oral/palatal pruritus • oral/palatal tingling • nausea • drooling	• nasal symptoms • throat pruritus			
I ANAPHYLAXIS							
II ANAPHYLAXIS			• crampy abdominal pain • sudden and/or recurrent vomiting • diarrhea	• feeling of difficult breathing • hoarseness	• sudden repetitive cough • chest tightness • mild to moderate bronchospasm	• sudden change in behavior or activity level • presyncope e.g. dizziness, weakness	
III ANAPHYLAXIS				• upper airway angioedema e.g. tongue swelling, throat tightness, difficulty swallowing, odynophagia • stridor	• severe bronchospasm (not responding or worsening despite treatment)	• confusion • somnolence • feeling of impending doom	• sudden relevant hypotension ‡ • pale & floppy child • short episode of collapse • syncope
IV ANAPHYLAXIS					• respiratory failure†	• loss of consciousness (non-transient)	• cardiovascular failure • cardiac arrest

* Consider lower threshold of epinephrine in the case of previous severe reaction or co-existent asthma, or exposure to patient-relevant allergen^{10,12}

† The severity grade is defined by the most severe symptom

‡ Hypotension is defined as systolic blood pressure: 1 month to 1 yr < 70 mmHg; 1-10 yrs < 70 mmHg; 11-17 yrs < 90 mmHg⁸