Anaphylaxis severity grade assessed by five different classifications.

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Abstract

Background – While the definition of anaphylaxis is clear, its grade of severity remains a subject of debate, especially since different published classifications provide different grading score, and the same reaction may not receive the same score from different classifications. The objective of this study was to evaluate the possible discrepancies in severity scoring system for anaphylaxis in patients with a positive food challenge (OFC), using the WHO for the 11 th version of the International Classification of Diseases (ICD-11) as the main reference. Methods – We conducted a retrospective observational study at the University Hospital of Montpellier, France, including patients with a positive OFC, between 2018 and 2022. We classified the severity of each reaction, as per the ICD-11 classification, but also as per four other widely used and validated classifications for grading anaphylaxis severity. Results – 235 patients presented a positive OFC between January 2018 and December 2022: 143 suffered from anaphylaxis, according to the ICD-11 classification. 76.2% of them were classified as grade 2 according to the ICD-11 classification, and 23.8% as grade 3. When comparing the different classifications, a complete concordance was recorded in 8 patients (5.6%) only. All classifications showed a good sensitivity (ranging from 99.3 to 100%), but different specificity (from 67.4 to 93.5%), and discrepancies between them were shown in most patients. Conclusion – Our work highlights the need to refine the different scoring systems, to accurately capture anaphylactic reactions and ensure appropriate management, and, in the end, to adopt a universal, intuitive, and easy-to-use classification, such as the ICD-11 one.

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Methods – We conducted a retrospective observational study at the University Hospital of Montpellier, France, including patients with a positive OFC, between 2018 and 2022. We classified the severity of each reaction, as per the ICD-11 classification, but also as per four other widely used and validated classifications for grading anaphylaxis severity.

Results – 235 patients presented a positive OFC between January 2018 and December 2022: 143 suffered from anaphylaxis, according to the ICD-11 classification. 76.2% of them were classified as grade 2 according to the ICD-11 classification, and 23.8% as grade 3. When comparing the different classifications, a complete concordance was recorded in 8 patients (5.6%) only. All classifications showed a good sensitivity (ranging from 99.3 to 100%), but different specificity (from 67.4 to 93.5%), and discrepancies between them were shown in most patients.

Conclusion – Our work highlights the need to refine the different scoring systems, to accurately capture anaphylactic reactions and ensure appropriate management, and, in the end, to adopt a universal, intuitive, and easy-to-use classification, such as the ICD-11 one.

Keywords: adrenaline; anaphylaxis; classifications; ICD-11; severity.

Introduction

Anaphylaxis is the most severe immediate hypersensitivity reaction, which may potentially result in the death[1]. In 2013, Panesar reported an incidence of anaphylaxis between 1.5 and 7.9 per million inhabitants per year[2]. Although the number of deaths due to anaphylaxis remains low, the frequency of anaphylactic cases and of cases at-risk of anaphylaxis has been increasing in recent years[3].

The clinical definition of anaphylaxis remains the involvement of at least 2 organs (cutaneous signs, respiratory symptoms, digestive symptoms), as initially described by Ring and Messmer in 1977[4], and later adapted by other publications, including the one from the World Health Organization (WHO) for the International Classification of Diseases (ICD)-11[5]. A recent definition is that anaphylaxis is a serious allergic reaction that occurs rapidly and can result in death[6]. As for the classification of the severity of an anaphylactic reaction,

such topic remains a matter of debate. In recent years, several classifications emerged, enriching the existing ones, such as those from the ICD-11[7], the CoFAR one[8], or those by Sampson[9], Muraro[10], and Blazowski[11], and provided different scores to grade the severity of an allergic anaphylactic reaction.

These different classifications allowed a major advancement in the management of anaphylaxis (guiding the early use of adrenaline), however, differences between them perpetuate a lack of uniformity in grading different levels of severity, and consequently, potential differences in the therapeutic approach to patients experiencing the reaction. In clinical practice, the proliferation of classifications led to a lack of reproducibility, as the same reaction may not receive the same score from different classifications, which may then impact both the timing and the choice of a specific treatment.

The objective of this study was to evaluate the possible discrepancies in severity scoring system for anaphylaxis by applying them in patients who presented a positive food challenge, in the Allergy Unit of a University Hospital, using the WHO for the 11thversion of the International Classification of Diseases (ICD-11) as the main reference.

Methods

We conducted a retrospective observational monocentric study at the Allergy Department of the University Hospital of Montpellier, France. We included all patients – adults and children – who underwent a positive oral food challenge (OFC) for an IgE mediated food allergy, between January 2018 and December 2022. OFCs were performed following PRACTALL recommendations[12].

The study was approved by the Institutional Review Board of Montpellier (IRB-MTP_2022_09_202201201).

Patients' characteristics and information were extracted from the Food Allergy and Hypersensitivity Database® (FAHD). In case of missing data, a manual extraction was performed from the patient's electronic and/or paper medical records. For each patient, the following data were collected: age, sex, clinical manifestations experienced during the reported clinical history, symptoms presented during the OFC, severity of the reaction according to different classifications and administered treatment.

We manually reclassified the severity of all reactions according to 5 classifications of food allergy-related anaphylaxis, published in the literature (ICD-11; CoFAR; Sampson; Muraro; Blazowski)[7-11]. We chose to use the ICD-11 classification[7] as the reference one. Two independent allergists classified the severity of each reaction. Any disagreement between the two allergists was resolved through discussion with a third specialist to reach a final consensus.

The primary objective of the study was to evaluate the grading of a reaction considering the different classifications. Secondary objectives included the assessment of symptoms presented by patients during a positive OFC, compared with those reported in the patients' initial clinical history, and the evaluation of the appropriateness of adrenaline injection, according to the severity of the symptoms and based on the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI)[13].

Qualitative variables were evaluated as frequencies and percentages, and the quantitative variables were evaluated as median and interquartile range. Spearman's correlation coefficient was used to examine the correlation between the different classifications, and the gold standard (ICD-11 classification). ROC (Receiver Operating Characteristic) curves were plotted, with sensitivity, specificity, area under the curve (AUC), and corresponding optimal thresholds used to evaluate the diagnostic performance of each classification. AUCs were compared by the DeLong test. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Baseline Demographics

235 patients presented a positive OFC between January 2018 and December 2022: 143 suffered from anaphylaxis, according to the ICD-11 classification. The median age was 9 years both in the whole population

and in the subgroup of patients with anaphylaxis.

45 patients (31.5%) in the anaphylaxis group already experienced anaphylaxis during their clinical history when exposed to the culprit food, while 16 (17.4%) had a history of initial anaphylaxis but did not experience anaphylaxis during the positive OFC (*p-value*< 0.02). Eighty-three (35.3%) had no initial medical history with the tested food, and, among them, 49 patients (59.0% of this group) reacted with anaphylaxis, constituting 34.3% of all anaphylaxis cases. 102 patients (71.3%) presented a more severe reaction during the OFC, if compared to the one recorded in their clinical history. This group includes 98 patients transitioning from grade 1 to anaphylaxis, and 4 transitioning from anaphylaxis to anaphylactic shock.

Symptoms, treatment, and main allergens

Urticaria was reported by 56 patients in the anaphylaxis group (39.2%) as being present during the initial reaction to the food, compared to only 17 patients in the non-anaphylaxis group (18.5%) (*p-value*< 0.0008). The symptom most frequently presented in the anaphylaxis group was abdominal pain (60.8%), followed by urticaria (49.0%). Other patients' characteristics are shown in Table 1.

Most patients with anaphylaxis were treated with oral antihistamines (93.7%) and oral corticosteroids (69.2%); adrenaline intramuscular injection was administered only in 47.6% of them (Table 2).

When considering the most frequent food responsible for a positive OFC, the main group includes tree nuts (31.9%), followed by peanuts (27.7%) and eggs (11.1%) (Figure 1). As for tree nuts (Figure 1), cashew nuts were the most commonly one responsible for allergies (22.7% of this subgroup and 7.2% of the whole anaphylaxis group).

We assessed the different foods responsible for reactions during the OFC and found legumes (besides peanut) were those more frequently associated with anaphylactic reactions compared to non-anaphylactic ones (90.9% vs. 9.1%), while patients with a positive OFC to seafood, excluding fishes, reacted mainly without experiencing anaphylaxis (30.0% vs. 70.0%), as shown in Figure 2. Peanuts, the most common allergen associated with a positive OFC, were responsible for anaphylaxis in allergic patients in 70.8% of cases. As for tree nuts, almonds triggered anaphylaxis in every positive OFC; on the other hand, Brazil nuts, in the case of a positive OFC, were never associated with anaphylaxis (Figure 2).

Classification of the reactions

In the group of patients who experienced anaphylaxis during the OFC, more than three quarters of patients (76.2%) were classified as grade 2 according to the ICD-11 classification, and 34 patients (23.8%) were classified as grade 3. Distribution of patients according to the severity of the reaction, based on the different classification is shown in Table 3.

When comparing the different classifications, a complete concordance between all 5 of them, as for severity grading, was recorded in 8 patients (5.6%) only. Differences between classifications are shown in the Supplementary Table 1.

The sensitivity and specificity of the different classifications, for identifying anaphylaxis are shown in Table 4: sensitivity resulted the best for the classification of Muraro, Sampson, and Blazowski (100%), while specificity was the best for the one of Muraro (93.5%).

The determination of the area under the curve (AUC) showed that all classifications had a good ability to detect anaphylaxis. In the ROC analysis, the AUCs of CoFAR, Muraro's, Blazowski's and Sampson's classifications were 0.83, 0.97, 0,95 and 0.93, respectively. The DeLong test showed a significant difference between the AUCs of the ICD-11 classification and those of CoFAR (*p-value* 0.0001), Muraro (*p-value* 0.0117) and Sampson (*p-value* 0.001) classifications.

Discussion

Anaphylaxis management and severity labeling is still a subject of debate in 2024, even within a specialized allergy department. The lack of a unanimous international consensus and the multiplicity of published

classifications complicate the management of patients in an emergency setting. To our knowledge, this study is the first one comparing different classifications of anaphylaxis and severity levels by using the WHO classification proposed for the ICD-11[7] as the reference one. The results of this study demonstrate a certain degree of variability in anaphylaxis classification systems and therefore their implications for treatment management.

Given the multiple definitions of anaphylaxis, several groups proposed severity scores, often based on expert opinions, but only few of them have been validated[14-17]. In our study, each one of the 4 assessed classification provided different degrees of severity, when compared with the ICD-11 one. It is clear that the grading value differ, depending on the evaluated classification: indeed, Muraro's classification[10] has 3 levels of severity, Blazowski's one[11] has 4, while those from CoFAR[8]and Sampson[9] go from 1 to 5. Therefore, in clinical practice, when a patient presents, for example, a reaction classified as a grade 2 anaphylaxis, this could have a different meaning, following the used classification, including different possible symptoms and organs involved, and thus a different therapeutical approach. In his paper, Blazowski already highlighted the discrepancy between several classifications, some of them not necessarily used to classify food-induced anaphylaxis, and he underlined that a new severity grading system was needed, especially to harmonize the definition of severity and to avoid any delay in the administration of adrenaline[11]. Our work underlines the importance of using the same classification in a work unit and of communicating which one is employed, to better approach patients. Also, it would be helpful to internationally use the same grading system, to better inform and exchange clear information on patients between physicians. We decided to refer to the ICD-11 classification as a gold standard since it's the one used on a daily base in our unit, and it's easy to use; it is also the classification used by the WHO post-coding system, which is already used and will be even more implemented over the coming years, being available in all countries for all healthcare professionals and will therefore allow to identify even cases coded by non-allergists, especially primary care physicians.

Our study is based on oral food challenge results, during which vomiting is a common symptom, often combined with other symptomatic elements warranting the injection of adrenaline[18]. The most frequently reported symptom during OFC in our anaphylactic patients was abdominal pain. This result is noteworthy because abdominal pain is not always considered as one of the main symptoms of anaphylaxis. Also, in some countries as in the UK and Australia[19], abdominal symptoms are not considered in the classification of food allergy reactions. However, the results of our study show that abdominal pain is often the first symptom found in patients further developing anaphylactic reactions. Therefore, the question arises as to whether this reported symptom should be considered as a red flag for a possible anaphylactic reaction. In our gold standard classification (ICD-11), it accounts for one organ involvement (the gastro-intestinal track). 98 patients (41.7%) developed anaphylaxis during the oral provocation test, while none of them had a clinical history of severe reaction. Main foods associated with a worsening of the reaction, compared with the one reported in patients' clinical history, were peanuts (28.8% of patients), eggs (12.0%), and pistachios (8.0%). On the other hand, considering patients with a history of anaphylaxis, 45 (19.5%) presented an anaphylactic reaction during the OFC, while 16 (7%) did not. These data underline the fact that the evolution of a food allergy remains often unpredictable, and OFC should be performed only by well trained professionals, in a safe hospital environment.

Regarding the management of patients, our study revealed a delay, or even an absence, in the use of adrenaline in cases of anaphylaxis, regardless of the classification used by the physician. A study by Eller et al.[20] emphasizes the existence of different severity grading systems for anaphylaxis and the use of adrenaline, leading to variations in its administration, if based on the grading system. There are no universally validated diagnostic tools to determine which symptoms warrant adrenaline treatment compared to those that do not[21], which may explain the underuse of adrenaline found in our study. A recent study highlights the underuse of adrenaline even in pediatric emergency services in France[22]. Such issue poses a problem in many healthcare institutions, even within a specialized allergy service, which may be explained by two major factors: a lack of training in anaphylaxis management and hesitancy among healthcare professionals to use adrenaline (due to a fear regarding the bathmotropic effects of adrenaline) as well as simply a lack of recognition of anaphylactic reactions[23]. Additionally, the multitude of existing classifications and their perceived complexity may also

contribute to a less clear indication for such a vital treatment. What physicians should remember is that adrenaline is the key treatment of severe allergic reaction, and that its injection during a positive OFC is safe, even when not strictly needed[24]. At the same time, most adverse reactions to the intramuscular injection are not serious and are transient, while the risk for a patient experiencing anaphylaxis may raise up to a possible fatality. These factors show that the risk-benefit ratio is strongly in favor of the use of adrenaline to promptly treat any anaphylactic reaction. At last, as for treatment of the reaction, we recorded a statistical difference in the use of corticosteroids, during an anaphylactic reaction. Even though such a therapeutical approach is not recommended[5], we could speculate that the fear of not providing enough treatments wrongly pushed the physicians in including glucocorticoids in the list of the administered ones.

Our study presents some limitations: it is a retrospective study, and some data may therefore be missing from the medical records of certain patients. Also, the choice to use the ICD-11 classification as the reference one, well-justified for its ease of use in daily practice and its validation by the WHO as stated above, could potentially introduce biases. Nevertheless, we also present results that show a certain strength, considering the number of included patients, the double-blind verification of the classifications by two specialized allergists, and the use of four recent classifications for comparison purposes.

While the emergency of different classifications of anaphylaxis and of its severity is a real asset for clinical management, their multiplicity create confusion among healthcare professionals. Therefore, it would be important to consider consolidating these different classifications into one that is both appropriate and intuitive, favoring sensitivity with a good compromise regarding specificity. Our work highlights the need to refine theses scoring systems, to accurately capture anaphylactic reactions and ensure appropriate management, without neither over- nor under-treat patients. In conclusion, there is a real need to adopt a universal, intuitive, and easy-to-use classification, such as the ICD-11 one, while destigmatizing at the same time the use of adrenaline.

Key message

Physicians need to easily communicate between them on anaphylaxis, without risking misunderstanding the severity of a reaction. The multiple existing classification do not allow a univocal grading of the severity of anaphylaxis. An easy approach is needed, as the one proposed by the WHO, which will be also used by non-specialist to classify anaphylactic reactions.

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Tables

Table 1 – Characteristics of the included population.

	Anaphylaxis	**No**
	N = 143	**N=**
Sex, males, n (%)	91 (63.6)	59
Age (year), median (Q1-Q3)	9 (6-13.5)	9.5

	Anaphylaxis	**No**
Previous/Initial clinical history, n (%)	**Previous/Initial clinical history, n (%)**	**Pr**
Anaphylaxis	45 (31.5)	16
Urticaria	56 (39.2)	17
Generalized oedema	47 (32.9)	31
Pruritus	11 (7.7)	9 (
Sneezing	0 (0)	1 (
Rhinitis	6 (4.2)	2 (
Oedema of larynx	5 (3.5)	2 (
Cough	19 (13.3)	5 (
Dyspnea	5 (3.5)	5 (
Dysphonia	4 (2.8)	0 (
Conjunctivitis	1 (0.7)	0 (
Abdominal pain	16 (11.2)	9 (
Vomiting	23 (16.1)	7 (
Nausea	3 (2.1)	2 (
Hypotension	4 (2.8)	2 (
Asthenia	0 (0)	2 (
Tachycardia	1 (0.7)	0 (
Clinical reaction during oral food challenge, n (%)	**Clinical reaction during oral food challenge, n (%)**	**Cl**
Anaphylaxis	143 (100)	92
Urticaria	70 (49.0)	37
Generalized oedema	19 (13.3)	14
Localized Pruritus	43 (30.1)	39
Generalized Pruritus	3 (2.1)	1 (
Sneezing	2 (1.4)	0 (
Rhinitis	56 (39.2)	29
Oedema of larynx	3 (2.1)	0 (
Cough	47 (32.9)	3 (
Dyspnea	10 (7.0)	0 (
Wheezing	11 (7.7)	2 (
Dysphonia	2 (1.4)	0 (
Conjunctivitis	8 (5.6)	10
Abdominal pain	87 (60.8)	28
Vomiting	54 (37.8)	4 (
Nausea	56 (39.2)	5 (
Diarrhea	6 (4.2)	1 (
Hypotension	17 (11.9)	0 (
Asthenia	6 (4.2)	0 (
Tachycardia	5 (3.5)	0 (

Table 2 – Treatment administered upon reaction, during the oral food challenge, in the 235 patients.

	Anaphylaxis	**Non anaphylaxis**	p-value
	N = 143	**N= 92**	
Oral glucocorticoids	98 (68.5)	31 (33.7)	< 0.001
Oral antihistamines	135 (94.4)	74 (80.4)	*0.001*
Intramuscular adrenaline	68 (47.6)	4 (4.3)	< 0.001
Salbutamol	36 (25.2)	8 (8.7)	*0.002*

	Anaphylaxis	**Non anaphylaxis**	p-value
Antihistamine eye-drops	2 (1.4)	8 (8.7)	*0.02*

Table 3 – Distribution of anaphylactic and non-anaphylactic patients, following the 5 assessed classifications, based on the severity of symptoms.

	Anaphylaxis	**Non anaphylaxis**	
	N = 143	**N= 92**	
ICD-11[7] classification, n (%)	**ICD-11[7] classification, n (%)**	**ICD-11[7] classification, n (%)**	
Grade I	0 (0)	92 (100)	
Grade II	109 (76.2)	0 (0)	
Grade III	34 (23.8)	0 (0)	
Grade IV	0 (0)	0 (0)	
CoFAR[8] classification, n (%)	**CoFAR[8] classification, n (%)**	**CoFAR[8] classification, n (%)**	**Mura**
Grade I	1 (0.7)	62 (67.4)	Grade
Grade II	97 (67.8)	27 (29.3)	Grade
Grade III	28 (19.6)	3 (3.3)	Grade
Grade IV	17 (11.9)	0 (0)	Grade
Sampson's[9] classification, n (%)	**Sampson's[9] classification, n (%)**	**Sampson's[9] classification, n (%)**	**Blazo**
Grade I	52 (36.4)	81 (88.0)	Grade
Grade II	45 (31.5)	8 (8.7)	Grade
Grade III	33 (23.1)	3 (3.3)	Grade
Grade IV	13 (9.1)	0 (0)	Grade

Table 4 – Sensitivity and specificity of the evaluated classification, when using the ICD-11[7] as the reference one.

Classification	**Sensitivity**	**Sensitivity**	**Specificity**	**Specificity**
CoFAR[8]	99.3%	95% CI: 0,97-1,00	67.4%	95% CI: 0,57-0,76
Sampson[9]	100%	95% CI: 1,00	85.9%	95% CI: 0,78-0,92
Muraro[10]	100%	95% CI: 1,00	93.5%	95% CI: 0,78-0,92
Blazowski[11]	100%	95% CI: 1,00	91.3%	95% CI: 0,85-0,97

Legend – CI: confidence interval.

Figures

Figure 1 – Distribution of foods causing any allergic reactions in our group of 235 patients (A) and in the subgroup of 143 anaphylactic patients.

Figure 2 – Distribution of anaphylactic and non-anaphylactic reactions recorded during the oral challenge, with main tested foods (A) and with tree nuts (B).

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