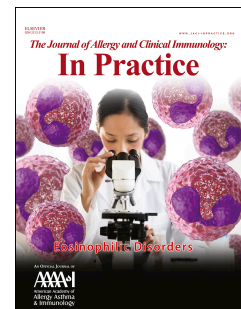


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Reproducibility of symptom sequences across episodes of recurrent anaphylaxis

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Abstract (250 words)

Background: Anaphylactic reactions may present with varying levels of severity, ranging from mild multisystem involvement to severe, and sometimes fatal, anaphylaxis. The severity of anaphylaxis is variable from one reaction to the next within the same individuals.

Objective: To compare the temporal sequence of symptoms within individuals and between individuals across multiple anaphylactic reactions.

Methods: Patients were evaluated for recurrent anaphylaxis in a tertiary care allergy clinic between 2012-2018. At each visit, patients were asked to record the temporal sequence in which symptoms of anaphylaxis appeared. These data were recorded at each visit and retrieved through retrospective chart review. Patients with a history of ≥ 2 anaphylactic reactions were included; those with anaphylaxis due to multiple allergens were excluded. The Fleiss' Kappa method was used to assess reproducibility of the order of appearance of specific symptoms during anaphylaxis within individual patients and between individuals with similar triggers.

Results: Mean patient age was 35.6 years (SD=13.9; range 1 – 68) of whom 113/149 (76%) were female. The mean Fleiss Kappa reproducibility score within individuals was 0.94, 5th percentile was 0.53 and 95th percentile was 1.0. The mean Kappa score between individuals was -0.03 [range, -0.14 to 0.05]. Among the 16/149 patients who recorded reactions of varying severity grades, the mean within-patient Kappa score was 0.96.

Conclusion: Individual patients experience reproducibly stereotypic anaphylactic reactions over time, that are unique to a given patient, irrespective of the cause of anaphylaxis, including foods, medications, mast cell disorders and idiopathic anaphylaxis. In contrast, symptom sequences during anaphylaxis are not reproducible between individuals.

Highlight Boxes

What is already known about this topic? For patients undergoing two consecutive peanut challenges, the same cluster of organ systems was involved in individual patients, but differed between patients.

What does this article add to our knowledge? We have extended the above observations and demonstrated that individuals with recurrent anaphylaxis experience stereotypic reactions with respect to the order of appearance of symptoms.

How does this study impact current management guidelines? By recognizing the stereotypic nature of anaphylactic reactions, especially the earliest symptoms, patients will be better able to identify incipient multisystem reactions and intervene appropriately with self-administration of epinephrine and activation of emergency medical services.

Keywords: anaphylaxis; food; epinephrine; systemic mastocytosis; stereotypic; sequence; manifestations; medication; idiopathic

Abbreviations: NSAIDs (nonsteroidal anti-inflammatory drugs), PAF (platelet activating factor), SD (standard deviation), IQR (Interquartile range)

Introduction

The lifetime prevalence of anaphylaxis is estimated to be up to 5% in the US population (1), with an incidence of 10-60 per 100,000 person-years (2-5). Longitudinal studies have found significant increases in the incidence of anaphylaxis over the past few decades (4-5). The effects of anaphylaxis on quality of life are far-reaching, affecting interactions at home, school and work, and limiting the ability to engage in diverse and formative life experiences such as travel and dining (6). Furthermore, findings of post-traumatic stress disorder, fear and anxiety are especially prevalent amongst those who have experienced more serious episodes of anaphylaxis (6).

Hymenoptera venom anaphylaxis is a common cause of severe and potentially fatal anaphylaxis in adults, especially middle-aged males (7,8). In infants and young children, foods including egg and cow milk are the most common triggers (9). Clonal and non-clonal mast cell disorders and hereditary alpha tryptasemia are increasingly recognized as causes of anaphylaxis across all age groups (10,11).

Although acute elevation of mast cell tryptase is the best serologic biomarker for diagnosis of anaphylaxis, some individuals experience reactions without a significant increase in serum tryptase (6,12). Other biomarkers and pathways may be involved, such as those involving platelet activating factor (PAF) (13). PAF levels were directly correlated with severity of anaphylaxis, whereas deficiency of PAF acetylhydrolase, the enzyme that inactivates PAF, was associated with severe and fatal anaphylaxis, (13,14).

Several broad patterns of anaphylaxis have been recognized, including uniphasic, biphasic and protracted reactions. Individual patients may present with varying grades of severity of anaphylaxis, ranging from mild multisystem involvement to severe and, rarely, fatal anaphylaxis. The severity of reactions may vary from one occurrence to the next, and individuals may have difficulty in anticipating when a reaction may become more severe, leading to hesitation in initiating appropriate treatment. Delays in administration of epinephrine have been shown to increase the likelihood of biphasic and protracted reactions, as well as death (15,16). For these reasons, early recognition and treatment are essential for optimal management of anaphylaxis.

In this study, we sought to examine the temporal sequence of manifestations of anaphylaxis within individuals and between individuals over the course of multiple reactions. Specifically, multisystem reactions were assessed with respect to the reproducibility of the order of appearance of signs and symptoms of anaphylaxis within a large cohort of patients.

Methods

We studied a cohort of patients with recurrent anaphylaxis who were seen in our outpatient tertiary care allergy clinic at St. Michael's Hospital, Toronto, Canada. A retrospective chart review was undertaken of patients assessed between January 1st, 2012, and December 31st, 2018, and demographic and clinical data were extracted. The study was approved by the St. Michael's Hospital Research Ethics Board.

Electronic records were searched using key words including “recurrent”, “anaphylaxis”, “multisystem” and “stereotypic”. The diagnosis of anaphylaxis was made based on the 2006 consensus criteria (2). Patients with a well-documented and unequivocal history of at least two anaphylactic reactions were included where (i) a single anaphylactic trigger was identified or (ii) patients had an underlying clonal mast cell disorder or (iii) patients were diagnosed with idiopathic anaphylaxis after other causes were ruled out by exhaustive investigations. Individuals of all ages were included.

In order to obtain reaction sequences, patients were asked to describe their reaction by listing the symptoms in the order of appearance. All patients included in this study were assessed by the same clinician (PV). Prior to 2012, it had been noted that patients had experienced symptom sequences that appeared to be reproducible from one reaction to the next. Subsequently, all patients with anaphylaxis were asked to delineate the symptom sequences in initial and follow-up visits, and these symptom sequences were recorded at each visit. Patients were instructed to schedule an appointment after experiencing a reaction.

The following patient data were extracted from the medical records by three independent reviewers, who were undergraduate (CS) or medical students (AM, MD) at the time: the age at first anaphylactic reaction, the course of each anaphylactic reaction, including order of appearance of symptoms, timing of pharmacologic interventions, and the type of anaphylactic trigger, including foods, medications, mast cell disorders and *Hymenoptera* insect stings. The same reviewer assessed all reactions for a given patient. Data were reviewed by the senior author. The grading system by Brown (17) was used to classify the reaction severity into mild

(grade 1), moderate (grade 2), and severe (grade 3) based on the severity and extent of organ system involvement for each reaction. These grades correspond to cutaneous involvement only (grade 1), respiratory or gastrointestinal involvement (grade 2), and hypoxia, hypotension and neurologic compromise (grade 3), respectively.

Statistical Analysis:

Continuous data were summarized using mean and standard deviation (SD) or mean and interquartile range (IQR) as appropriate. Categorical variables were summarized using frequency and percent. The Fleiss' Kappa reproducibility score (FKRS) (18) is a measure of agreement between categorical ratings. In this context, the FKRS was used as a measure of agreement with multiple episodes each with a categorical score. The Fleiss' Kappa method was used to assess the reproducibility of the order of appearance of specific signs and symptoms during anaphylactic reactions in individual patients. Kappa values between 0.8 to 1.0 represent near perfect levels of agreement between sequences. As the number of signs and symptoms varied over the different episodes of anaphylaxis within each individual, the lesser number of symptoms was used in the calculation of the Kappa statistic. Online Repository Text I describes an exemplar calculation of the Kappa statistic, demonstrating a patient with good agreement and one with poor agreement. The Kappa values of each individual were aggregated into a mean Kappa and its distribution was described. In a similar fashion, Fleiss' Kappa was used to assess the reproducibility of the order of signs and symptoms between patients with the same triggers. Amongst patients with anaphylaxis to foods, patients were further subdivided into categories of specific food allergies,

for example, peanut or shellfish. Those with an individual Kappa value ≥ 0.8 (near perfect agreement) were included in the between-patient Kappa statistic. Two between-patient approaches were carried out: one using individuals' episodes with the lowest number of symptoms, and the other using the episodes with the highest number of symptoms. Should any individual within a trigger category have every episode of identical sequence length, this would make the between-patient Kappa statistic congruent under both approaches mentioned above. Lastly, the agreement of symptoms within individuals with episodes that had more than one level of severity was examined. For each individual, one symptom sequence from each severity level was obtained and Fleiss' Kappa was used to examine the agreement of each episodic reaction across the severity levels.

Results

A total of 164 patients were identified with multiple documented episodes of anaphylaxis, of whom 6 were excluded for having more than one allergic trigger, and 9 excluded as having allergic reactions that did not meet criteria for anaphylaxis (Figure 1). The median age (SD) at first visit was 35.59 (13.87) years; eleven (7.4%) patients were <18 years; sex distribution was female 113/149 (75.8%) and the median number (IQR) of anaphylactic reactions per person was 6 (3-15) (Table 1). One hundred and sixteen of 149 (77.9%) patients had at least one grade 2 reaction and 33 (22.1%) patients had at least one grade 3 anaphylactic reaction. The three most common triggers of recurrent anaphylaxis in this cohort were food-induced anaphylaxis (n=29; 935 reactions), systemic mastocytosis (n=25; 722 reactions) and idiopathic anaphylaxis (n=47; 597 reactions) (Table II).

The within-patient Kappa values were similar for those whose cause of anaphylaxis was known (mean Kappa=0.957) as compared to those with idiopathic anaphylaxis (mean Kappa=0.896) (both near perfect levels of agreement).

The within-patient sequence agreement values were between 0.9 to 1.0 for 129 (86.6%) patients and equal to or greater than 0.5 (at least moderate agreement) for 144 (96.6%) patients (Table III). The between-patient tests using the episodes with the lowest and highest numbers of symptoms both yielded identical Kappa values. Contrary to the agreement present in the within-patient test, the between-patient sequence agreement values for specific allergic triggers ranged from -0.03 to 0.05, implying poor agreement (Table III). Sixteen individuals experienced reactions of multiple severity grades. In these 16 patients, all symptom sequences within a severity level were identical. Thirteen of sixteen (81.3%) patients had individual sequence agreement values of 1.0 and all 16 (100%) had values above 0.6 (Table IV). All individual allergy categories reported strong levels of agreement (Kappa>0.8) (Table V). Furthermore, strong levels of agreement were also present in individuals who reported ≤ 3 episodes (mean Kappa=0.88 (N=44)) and in those who reported ≥ 10 episodes (mean Kappa=0.96 (N=60)).

Discussion

In the course of clinical practice, we had anecdotally noted that individual patients tend to exhibit stereotypic sequences of symptoms during reactions of similar severity. We set out to formalize

these observations in a statistically rigorous manner. Using the Fleiss Kappa reproducibility score, we noted a very high degree of agreement between symptom sequences in patients experiencing multiple allergic reactions. The high measure of statistical agreement between the sequence of manifestations across multiple anaphylactic reactions indicates that these stereotypic reactions remain constant within individual patients in reactions spaced apart over months to years. In contrast, reproducibility scores between patients were low

Stereotypic sequences of symptoms during anaphylaxis were seen in our cohort of patients irrespective of the cause of anaphylaxis, including reactions triggered by foods, medications, clonal mast cell disorders and idiopathic anaphylaxis. Furthermore, the stereotypic nature of symptom sequences is equally present in patients with many episodes of recurrent anaphylaxis and in those with very sporadic episodes.

The majority of patients had reactions which were all clustered in one single severity grade. For those patients who experienced reactions of two or more severity grades, we analysed their manifestations for within-patient sequence agreement and still found strong reproducibility of individuals' previous symptoms. This suggests that regardless of how severe a reaction will become in its later stages, its initial stages are essentially identical, and in reactions of greater severity, additional symptoms are added on to the initial canonical sequence as additional organ systems are recruited as reactions progress and intensify. In this way, any given patient's manifestation of anaphylaxis can be described as a very specific continuum of symptoms which ranges from the initial symptoms to the most life-threatening signs such as hypotension and

airway compromise. A patient's anaphylactic reaction will start at the initial symptom and will proceed along their specific sequence until the progression of the reaction has halted.

In any given individual, several factors may come into play that determine which organ systems are affected during an anaphylactic reaction. The extent and rapidity of allergen delivery to an organ or organ system will depend on blood flow to that region. The density of the mast cell infiltration will also be a major determinant of local mediator production and release and the proximity of mast cells to blood vessels, smooth muscle and mucosal surfaces will have a major influence on the degree of organ system involvement during anaphylaxis (19). Release of mast cell mediators have the capacity to perturb normal organ system function with disruption of homeostasis. Local counter-regulatory mechanisms will be activated to override those changes with a return to homeostasis. The balance between mast cell mediator-induced dysregulation and countervailing homeostatic mechanisms will determine the degree of clinical decompensation in one or more organ systems.

The signs and symptoms experienced during an anaphylactic reaction are the result of the extent of perturbation from homeostasis. Arguably, the order of appearance of those signs and symptoms reflects the order of organ system involvement during a reaction. The extent and rapidity of mediator release will determine local organ system involvement in the microenvironment of the activated mast cells but spillover of mediators into the systemic circulation will also have the potential to perturb downstream organ systems. For example, mast cell activation in the airways may act locally on smooth muscle causing bronchospasm and similarly, mast cell activation in the coronary arteries may lead to coronary vasospasm resulting

in myocardial ischemia. Spill-over of high levels of mast cell mediators into the systemic circulation may affect distal organ systems as well, and these effects may be offset by activation of compensatory system-wide neuroendocrine mechanisms (20).

In a seminal study, Chong et al (21) compared organ system involvement and symptom severity in individuals undergoing peanut challenge. In patients undergoing two consecutive challenges, the same cluster of organ systems was involved in individual patients, but differed between patients. The authors speculated that the severity of organ system involvement was the net of mast cell density and mediator release and impairment of switch-off mechanisms (21), such as platelet activating factor acetylhydrolase deficiency (13). We have extended those findings to demonstrate that intra-individual stereotypic reactions occur in a specific temporal sequence in reactions occurring by accidental exposure to allergens in the community and involve reactions not only to peanut but to other foods, medications, clonal mast cell disorders and idiopathic anaphylaxis. Notably, there was no difference in reproducibility scores for individuals whose anaphylaxis was of a known cause as compared to those with idiopathic anaphylaxis. In contrast to the high degree of reproducibility of symptom sequences within individuals, the between-individuals analysis yielded low Kappa values for all causes of anaphylaxis, suggesting that stereotypic sequences are specific to individuals, but not a function of the cause of anaphylaxis.

A major limitation of this study is that stereospecific sequences reported by individual patients were subject to recall bias of their accounts of anaphylaxis. In those patients with severe anaphylaxis, the distress of rapidly progressive and increasingly severe reactions may lead to a lack of precision in the reporting of symptom sequences. Our results may not be generalizable to

either those experiencing anaphylaxis from multiple causes as these individuals were excluded from our study or to those experiencing anaphylaxis from *Hymenoptera* insect stings as only one such patient was included in our cohort. A formal sample size calculation was not performed as all available data were used for the analysis. Post-hoc power calculations often lead to flawed and incorrect results and therefore were not performed (22). The reviewers were not blinded to the study hypothesis, potentially leading to bias in interpretation of symptom sequences. However, the medical records clearly laid out the symptom sequences in detail. A noteworthy issue is that our study cohort is skewed to patients with mast cell disorders, including systemic mastocytosis and MCAS and to patients with difficult-to-manage recurrent anaphylaxis. For these reasons, the numbers of episodes of anaphylaxis are higher than may be seen in other clinical settings, the causes of anaphylaxis in this study population will differ from those seen in the general population and the frequency of return visits is also higher. Finally, the current study did not evaluate the response to therapeutic interventions during the course of anaphylactic reactions.

Using the Fleiss Kappa reproducibility score, we found that the temporal sequence of symptoms is stereotypic in individuals who experience recurrent anaphylactic reactions. Stereotypic sequences of symptoms are unique to a given patient. In contrast, symptom sequences during anaphylaxis are not reproducible between individuals.

These findings are significant inasmuch as they can be used to teach patients to recognize their specific temporal sequence of signs and symptoms, so as to be made aware that progression along their specific pathway of symptoms may require administration of rescue medication and additional medical intervention. This awareness will allow individuals to predict how future

reactions may manifest, while understanding that reactions may differ in severity. Recognizing patient-specific stereotypic sequences will be a move towards precision medicine in anaphylaxis, both in understanding patient-specific phenotypes and the appropriate timing of therapeutic interventions (23).

Word count= 2609

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Figure 1: Consort chart showing the sequential stages of participant inclusions and exclusions

Table I: Patient Characteristics

	Overall (N = 149)
Female N (%)	113 (75.8)
Age (years) at time of assessment (mean (SD))	35.59 (13.87)
	Range = 1 to 68
Child – [< 18 years of age] N (%)	11 (7.4)
Number of anaphylactic reactions per person (median [IQR])	6.00 [3.00, 15.00]
	Range = 2 to 503
Highest individual reaction severity* grade N (%)	
1	2 (1.3)
2	116 (77.9)
3	33 (22.1)

*According to Brown (14)

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Table II: Prevalence of different allergy types

Allergic trigger or cause of anaphylaxis	Number of individuals	Total number of reactions
Food	29	935
Systemic mastocytosis	25	722
Idiopathic	47	597
Cholinergic anaphylaxis	11	494
Catamenial anaphylaxis	9	120
Food-dependent exercise-induced	13	76
Exercise	5	47
Drugs	7	32
Latex	2	17
Hymenoptera stings	1	7

Table III: Kappa values within individuals (Group 1) and between individuals with identical allergic triggers (Group 2)

Cohort	Mean Kappa	SD	Minimum	25%	Median	75%	Maximum
Group 1	0.938	0.184	-0.094	1.000	1.000	1.000	1.000
Group 2	-0.033	0.053	-0.14	-0.059	-0.021	-0.009	0.049

Table IV: Kappa values within individuals with reactions of varying severity

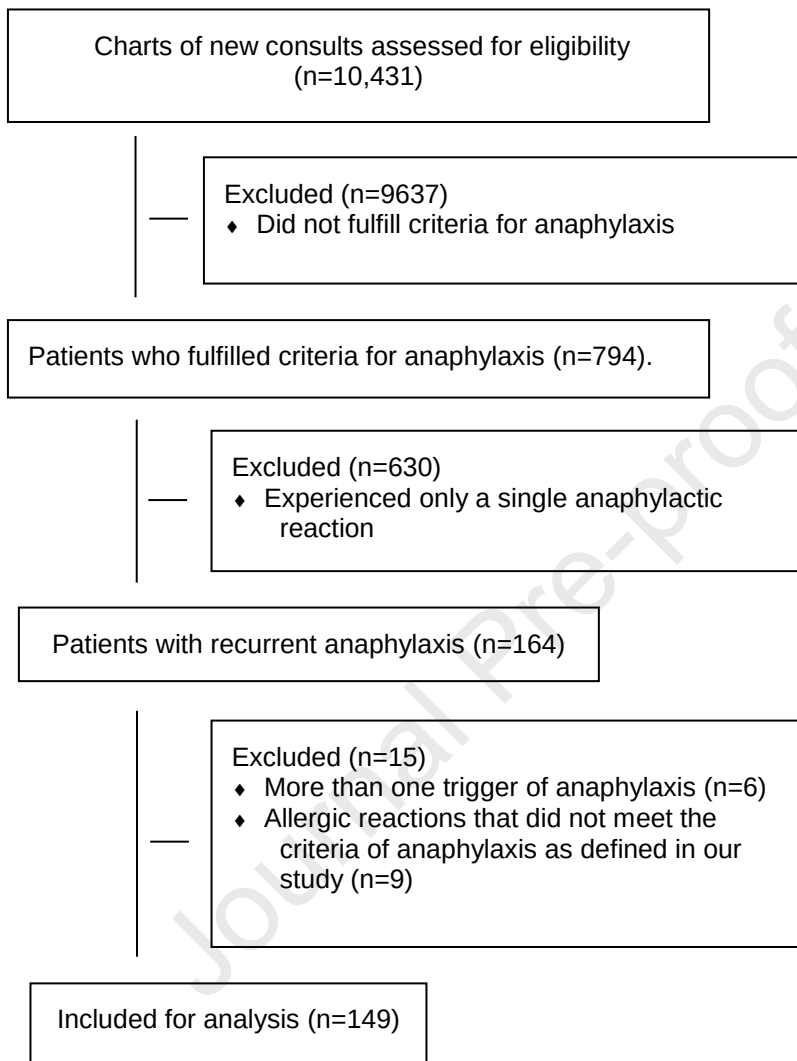
Mean Kappa	SD	Minimum	25%	Median	75%	Maximum
0.958	0.103	0.619	1.000	1.000	1.000	1.000

Table V: Kappa by allergy type

	Mean kappa	SD kappa	Median kappa
Food	0.910	0.194	1
Cholinergic anaphylaxis	0.979	0.059	1
Drugs	1.000	0.000	1
Hymenoptera sting	1.000	NA ¹	1
Exercise	1.000	0.000	1
Catamenial anaphylaxis	0.989	0.033	1
Latex	1.000	0.000	1
Systemic mastocytosis	0.981	0.064	1
Food-dependant exercise-induced	0.924	0.202	1
Idiopathic	0.896	0.259	1

¹Only one individual, therefore, no SD reported

Figure 1



Online repository text 1: Exemplar calculation of within-patient Kappa statistic

Ex 1: Patient with good agreement (Kappa = 1.00)

Reactions #1-5: Chest tightness → wheezing → hand swelling → facial swelling → generalized flushing

Reaction #6: Chest tightness → wheezing → hand swelling → facial swelling → generalized flushing → presyncopal sensation

Raters (reactions) = 6, Symptoms = 5

Categories (sequence step) = 5

	SeqStep 1	SeqStep 2	SeqStep 3	SeqStep 4	SeqStep 5
Chest tightness	6	0	0	0	0
Wheezing	0	6	0	0	0
Hand swelling	0	0	6	0	0
Facial swelling	0	0	0	6	0
Generalized Flushing	0	0	0	0	6

Ex 2: Patient with poor agreement (Kappa = -0.059)

Reaction #1: Trouble swallowing → tongue swelling → tingling palate → hoarse voice → inspiratory stridor → wheezing → chest tightness → shortness of breath

Reaction #2: Generalized hives → lip swelling → upper airway obstruction

Reaction #3: Generalized itching → Generalized hives → upper airway obstruction

Raters (reactions) = 3, Symptoms = 7

Categories (sequence step) = 3

	SeqStep 1	SeqStep 2	SeqStep 3
Trouble Swallowing	1	0	0
Tongue Swelling	0	1	0
Tingling Palate	0	0	1
Generalized Hives	1	1	0
Lip Swelling	0	1	0
Airway Obstruction	0	0	2
Generalized Itching	1	0	0