Otorhinolaryngology-Head and Neck Surgery

Review Article

ISSN: 2398-4937

From the lack of skin symptoms to the shortening of the latency interval – An attempt to include warning signals for severe anaphylaxis in a severity assessment tool

Alketa H. Bakiri[1,2], Anxhela Gurakuqi-Qirko[3,4], Doris Ç. Mingomataj[2], Dorela Luku[5], Odilija Rudzeviciene[6] and Ervin Ç. Mingomataj[5]*

[1]American Hospital of Tirana, Outpatients Service, Tirana, Albania

[2]Albanian University, Faculty of Medical Sciences, Tirana, Albania

[3]Deptartment of Biomedical and Experimental Sciences, University of Medicine, Tirana, Albania

[4]Division of Internal Medicine and Respiratory Function Lab, "Shefqet Ndroqi" University Hospital, Tirana, Albania

[5]"Mother Theresa" School of Medicine, Department of Allergology and Clinical Immunology, Tirana, Albania

[6]Vilnius University, Faculty of Medicine, Clinic of Children Diseases, Vilnius, Lithuania

Abstract

Background: Anaphylaxis represents the most immediate severe allergic reaction, and the need for early symptom recognition has led to the compilation of different clinical classifications.

The objective of review: We aimed to create a completed and easy-usable anaphylaxis severity assessment tool that includes some warning signs for disease severity and helps allergists and emergency caregivers in disease management.

Discussion: The overall severity either is defined by the highest numerical value of clinical symptoms. This instrument considers severe hypotensive events lacking skin symptoms after exposure to culprit allergen(s) more severe cases than identical reactions with skin symptoms. The abrupt hypotension may lead to failure of fluid extravasation and lack of mediators' concentration outside the cardiovascular system. The instrument also considers neurological symptoms and cardio/cerebrovascular disease risk factors for ineffective initial treatment, complications, and a warning signal to ask for intensive care unit personnel to assist the treatment team. Independently to cardiorespiratory symptoms, an evidenced short(er) time interval between allergen exposure and the successive reaction (compared to previous episodes) is considered an indicator for the subject's observation in the red area of the emergency unit because the clinical situation may worsen suddenly.

Conclusions: The potential incorporation of this instrument in the future severity assessment systems may help specialized caregivers recognize supplemental warning signals that account for possible disease worsening or complications and, therefore, allow them to avoid unnecessary fatal outcomes.

Introduction

Anaphylaxis, the most severe and life-threatening allergic reaction, is generally a systemic immunoglobulin E (IgE)-mediated reaction resulting from the sudden release of multiple inflammatory mediators from mast cells and basophils [1-3]. This acute pathology can involve several organ systems, particularly the skin, respiratory tract, gastrointestinal tract, and cardiovascular system, where mast cell concentrations are highest [3-7]. The action of mast cell and basophil mediators such as histamine, leukotrienes, and platelet-activating factor leads to smooth muscle contraction, vascular muscle relaxation, and an increase in vascular permeability, causing bronchiolar constriction, abdominal cramps, localized angioedema, hypoxia, significant loss of intravascular volume and shock in a short time [2,7-9]. Besides IgE-mediated reactions, non-immunologically mediated reactions leading to similar clinical symptomatology have been called 'anaphylactoid' or 'pseudo allergic.' They are now called 'non-immune anaphylaxis' according to a consensus of the World Allergy Organization (WAO) [3]. The most common elicitor in children is food, while drugs and insect venoms are the primary suspected inducers in adults [1,9-11].

The clinical diagnosis is based on experiencing specific symptoms from at least two organs or systems (airway, cardiovascular, gastrointestinal, or cutaneous) within proximity of allergen exposure [8,12]. Early symptoms' recognition and prompt therapy institution are central to a successful outcome because delays in epinephrine administration have been associated with fatalities [1,9,13]. The diversity of recognized symptoms has led to the compilation of different classifications helping clinicians to assess the disease severity (Table 1) [3-5,12-23]. Traditionally, four-grade classifications routinely place 'severe' anaphylaxis in grades 3 and 4 [3,14]. In 1959, Mueller put the respiratory symptoms in grade 3 and cardiovascular symptoms in grade 4 [4]. In 1977, Ring and Messmer classified respiratory and cardiac symptoms according to their severity in grades 2 or 3, and cardiorespiratory arrest in grade 4 [5]. Along recent decades, the need for standardized diagnostic criteria among anaphylaxis treating physicians

Correspondence to: Ervin Ç. Mingomataj, "Mother Theresa" School of Medicine, Department of Allergology and Clinical Immunology, Tirana, Albania, E-mail: allergology@gmx.de

Keywords: *abrupt hypotension, anaphylaxis, cardio/cerebrovascular comorbidity, lack of skin symptoms, latency interval, and severity assessment tool*

Received: May 03, 2021; **Accepted:** May 20, 2021; **Published:** May 26, 2021

Table 1. Chronological presentation of main approaches on the severity assessment for immediate allergic reactions.

Author(s), Year	Mild Allergic Reaction	Moderate Anaphylactic Reaction		Severe Anaphylactic Reaction (Shock)			Anaphylactic Shock or Clinical Death	
	Grade 1	Grade 2A	Grade 2B	Grade 3A	Grade 3B	Grade 3C	Grade 4	Grade 5
Mueller [4]	Urticaria, pruritus, malaise	Angioedema, chest tightness, nausea, vomiting, abdominal pain, dizziness		Dyspnea, wheeze, stridor, dysphagia, hoarseness			Hypotension, collapse, loss of consciousness, incontinence, cyanosis	-
Ring et al. [5]	Itch, flushing, urticaria, angioedema	Grade 1 + nausea, cramps, rhinorrhea, dyspnea, hoarseness, tachycardia (≥20/min), hypotension (≥20mm Hg drop in SBP), arrhythmia		Grade 1 + vomiting, defecation, laryngeal edema, bronchospasm, cyanosis, shock			Grade 1 + vomiting, defecation, respiratory arrest, circulatory arrest	-
Ring et al. [16]	Itch, flushing, urticaria, angioedema, redness, feeling warm,	Grade 1 + nausea, cramps, rhinorrhea, dyspnea, hoarseness, tachycardia, moderate hypotension (weakness), arrhythmia (palpitations), chest pain		Grade 1 + vomiting, defecation, laryngeal edema (throat), bronchospasm (wheezing), stridor, cyanosis, shock, altered level of consciousness			Grade 1 + vomiting, defecation, respiratory arrest, circulatory arrest	-
Sampson et al. [17]	Localized pruritus, flushing, urticaria, angioedema, oral pruritus, oral "tingling," mild lip swelling	Grade 1 + Generalized pruritus, flushing, urticaria, angioedema, nausea, emesis, nasal congestion, sneezing, change in activity level		Grade 1-2 + throat, chest tightness, tachycardia, anxiety			Grade 1-3 + hoarseness, "barky" cough, difficulty swallowing, dyspnea, wheezing, cyanosis, dysrhythmia, mild hypotension, "light headedness," feeling of "*pending doom*"	Grade 1-4 + loss of bowel control, respiratory arrest, severe bradycardia or hypotension, circulatory arrest, loss of consciousness
Cox et al. [18]	The affection of one system or generalized pruritus, urticaria, flushing, or sensation of heat or warmth, angioedema, sneezing, rhinorrhea, congestion, nausea, ocular erythema, or itching	The affection of more than one system or asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator), abdominal cramps, vomiting, diarrhea, uterine cramps		Asthma (e.g., 40% PEF or FEV1 drop NOT responding to an inhaled bronchodilator), laryngeal, uvula, or tongue edema with or without stridor			Respiratory failure with or without loss of consciousness or hypotension with or without loss of consciousness	Death
Mertes et al. [22]	Cutaneous signs: generalized erythema, urticaria, angioedema	Measurable but not life-threatening symptoms: cutaneous signs, hypotension, tachycardia, cough, difficulty inflating		Life-threatening symptoms: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm			Cardiac and/or respiratory arrest	-
Vetander et al. [21]	Sudden itching of eyes and nose, generalized pruritus, flushing, urticaria, angioedema, oral pruritus, oral ¢tingling¢, mild lip swelling, nausea or emesis, mild abdominal pain, nasal congestion and/or sneezing, rhinorrhea, throat pruritus, throat tightness, mild wheezing, chest tightness, tachycardia (increase >15 beats/min), change in activity level, anxiety, tiredness	Grade 1 + crampy abdominal pain, diarrhea, recurrent vomiting, hoarseness, cough, barky cough, swallowing or speaking difficulties, muffled voice, stridor, dyspnoea, moderate wheezing, 'Lightheadedness', feeling of 'pending doom', somnolence		Grade 1-2 + loss of bowel control, cyanosis or saturation, hypotension* and/or collapse, dysrhythmia, severe bradycardia and/or cardiac arrest, confusion, loss of consciousness			-	-
Niggemann et al. [19]	Local reactions: e.g. redness, swelling, pruritus	Urticaria, angioedema, flush, OR abdominal pain, vomiting, diarrhea	Urticaria, angioedema, flush, PLUS abdominal pain, vomiting, diarrhea	Cough, wheezing, stridor OR tachycardia, lowered blood pressure	Objective dyspnea, accessory muscles and/or shock	Respiratory arrest and/or cardiovascular arrest	-	-
Cox et al. [20]	Symptom(s)/sign(s) from 1 organ system present: urticaria and/or erythema-warmth and/or pruritus, other than localized at the injection site and/or tingling, or itching of the lips or angioedema (not laryngeal) or sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion and/or itchy throat and/or cough or conjunctival erythema, pruritus or tearing or nausea, metallic taste	Symptom(s)/sign(s) from 2 organ symptoms listed in grade I		Grade 1 + mild bronchospasm, e.g., cough, wheezing, shortness of breath which response to treatment and/or abdominal cramps and/or vomiting, diarrhea, uterine cramps			Grade 1/3 + severe bronchospasm, e.g., not responding or worsening despite treatment and/or laryngeal edema with stridor	Grade 1, 3 or 4 + respiratory failure and/or collapse/hypotension and/or loss of consciousness (vasovagal excluded)
Muraro et al. [23]	Isolated local allergic reactions of the skin or mucosa at the first contact with the allergen	Allergic reactions that involve skin away from the site of allergen contact, upper airway, and/or gastrointestinal tract		Severe, potentially life-threatening allergic reactions involving cardiovascular, neurological, bronchial, and/or laryngeal symptoms and signs			-	-

has led to the compilation of further classifications [10,15]. Among other approaches, chronologically Ring and Behrendt complemented previous attempts further with visceral symptoms (1999), Sampson was the first author ever that included neurological symptoms in the clinical classification (2003), and WAO proposed a uniform grading system to classify systemic allergy reactions after allergen immunotherapy and put nasal symptoms in grade 1 (2010) [16-18]. In contrast, Niggemann and Beyer classified only the objective clinical symptoms in 3 principal grades and additional subordinate ones (2016) [19].

Trying to be suitable for daily practice primarily in the emergency and intensive care units (ICU), the recently proposed instruments are generally characterized by few grades and valuable in different cases of anaphylactic reactions - independent to the allergen or inciting case [15,18,19,22,23]. Despite the progress on the standardization of clinical criteria, a broad group of allergology academics shared the opinion that a harmonized severity scoring system for acute allergic reactions is urgently needed [23].

Reflecting on these circumstances, this work aims to propose an actualized and practical tool on the severity assessment for anaphylactic reactions. It includes some early warning signals for severe anaphylaxis, such as the lack of skin symptoms, the short(er) latency interval, or the presence of vascular comorbidities, which are not shown in the previous anaphylaxis severity assessment tools. The contribution is addressed to medical personnel that manages (repeated) critical allergic reactions, such as allergists, specialists of emergency medicine, and ICUs. Including some warning signals for severe disease outcome, this tool considers that anaphylaxis after accidental exposure in non-controlled settings outside a hospital necessitates a relatively simple and completed classification system easy to apply retrospectively [15].

General considerations about the suggested attempt

Aiming to be a useful instrument on the severity assessment of anaphylactic reactions, the proposed classification in this work harmonizes both clinical and anamnestic data. It envisages two formats: 1) a numerical classification giving a continuum from mild to severe reactions clinically meaningful and helpful for allergy healthcare professionals, and 2) a four-grade-based ordinal format simple enough to be used and understood by other professionals and patients. Like other tools, the overall severity is defined by the highest numerical value of non-mandatory symptoms, i.e. most severe clinical symptoms [15,19]. In contrast to clinical data that assess the disease's severity, the included anamnestic details that were not shown by previous severity assessment tools serve only as warning signs for an (upcoming) severe reaction and a need for assistance by ICU caregivers because an immediate allergic reaction can be abruptly transformed into severe anaphylaxis.

Reflections on the first-ever included warning signals

The role of the cardiovascular affection on the lack of skin symptoms: The principal implication of the cardiovascular system during anaphylaxis may lead to severe systolic hypotension, inadequate organ perfusion, collapse, and circulatory arrest, especially after delays in epinephrine use or cases with a history of cardiovascular diseases [1,9,24-27]. Meanwhile, skin manifestations are also common symptoms in anaphylaxis [7-9]. Although urticaria as a usual symptom is at significantly high risk for moderate to severe anaphylaxis, about 7% of cases in adults occurred without skin manifestations [10,28]. Stoevesandt et al. [29] reported that venom immunotherapy build-up cycles complicated by moderate to severe anaphylaxis occurred more rapidly than mere urticaria. In contrast, Manivannan et al. [30] mentioned that patients who experienced repeated epinephrine administration were likely to present with wheezing, cyanosis, arrhythmias, hypotension, shock, stridor, laryngeal edema, cough, nausea, or emesis, and less likely to have urticaria [29,30]. Recently, Chapsa et al. [31] identified the absence of skin symptoms after the Hymenoptera sting as an independent predictor for severe anaphylaxis [31]. Additional causes of severe anaphylaxis without skin manifestations are cardiac anaphylaxis (Kounis syndrome), increased baseline tryptase level, and mastocytosis [31-34]. The shock in such critical situations corresponds to a combination of problems with cardiac function (the pump), intravascular volume (the tank), or systemic vascular resistance (the pipes), which lead to acute circulatory failure, decreased organ perfusion, inadequate delivery of oxygenated blood to tissues and resultant end-organ dysfunction [35,36]. The suddenly released inflammatory mediators due to circulatory basophils and abundant mast cells in anaphylaxis-involved organs/systems can lead to abnormal coronary spasms, myocardial depression and dysfunction, general vasodilation, and increased vascular permeability, causing significant loss of intravascular volume in a short time and, in unfortunate individuals, fatal outcome [2,7,9,33,37,38].

The mentioned above clinical and pathophysiological data indicate that anaphylaxis-related hypotension or cardiovascular collapse in the absence of skin manifestations should be considered a more severe episode than anaphylaxis cases announced by urticaria or local angioedema (grade 3B vs. grade 3A respectively, Table 2). Apart from diagnostic difficulties with concern to absent skin manifestations, the abrupt hypotension may lead to the failure of fluid extravasation despite the endothelial barrier breakdown, therefore being the cause of missed mediators' concentration outside the vascular system and, consequently, the reason for the inability to develop the initial urticaria or angioedema [9,17,26]. The eventual occurrence of skin symptoms only during/after a successful treatment agrees with the argument mentioned above. Consequently, the lack of skin affection in anaphylactic shock can be considered a signal of more severe disease than the cases with skin symptoms and a more serious situation that needs appropriate intervention and considering of ICU personnel assistance. These can include (multiple) uses of adrenergic therapy, great liquid infusion, oxygen therapy, increased doses of glucocorticoids, etc.

Respiratory system and asthma comorbidity: Being the most dangerous and potentially fatal, respiratory symptoms such as dyspnea that primarily affects children or young adults and the cardiovascular ones such as the severe hypotension or shock that primarily affect older subjects play a decisive role in anaphylaxis classification [9,15,17,19]. Respiratory symptoms result from the sudden release of multiple mediators such as cys-leukotrienes and bradykinin, leading to severe bronchoconstriction, laryngeal edema, and hypoxemia even in the case of pure local reactions in the anatomical proximity of the pharynx [1,8,24,39,40]. Meanwhile, an asthma history is associated with a higher risk for mortality during anaphylactic shock. An elevation of inflammation indicator FeNO (fractioned exhaled nitric oxide) is related to respiratory symptoms observed even in anaphylactic patients without asthma [41,42]. Consequently, the affection of lower airways needs an emergent treatment (epinephrine, oxygen, glucocorticoids, etc.). At the same time, the asthma comorbidity may be an alarming supplemental signal to ask ICU personnel to assist the treatment team.

The role of neurovascular and motor affection and cardio/neurovascular comorbidity: Severe anaphylaxis can be associated with local activation of the angiotensin system, which further induces arteriolar

Table 2. Severity classification of immediate allergic reactions [5,16-19,22], and warning signs for disease's severity [40,44,50].

A) Severity Classification of Immediate Allergic Reactions					
Affected Systems and Anamnestic Data	**Mild or Local Allergic Reactions**	**Moderate Systemic Anaphylactic Reactions**	**Severe Systemic Anaphylactic Reactions or Anaphylactic Shock**		**Clinical Death**
	Grade 1	**Grade 2**	**Grade 3A**	**Grade 3B**	**Grade 4**
Skin and Subcutis	Itching, flushing, rash, hives, local angioedema	Any of the left, accompanied by prodromal paresthetic sensations on palms and soles, as well as feeling of warmth	Any of the left, plus pallid face, cold extremities, sweat outbreak	Any of the Grades 2 or 3A, plus decreased body temperature; Grade 1 skin symptoms manifested ONLY during/after successful patient reanimation!	Any of the left
Abdominal Organs	-	Nausea, abdominal cramps (uterine, gastrointestinal, etc), anticipated by prodromal metallic taste, labial paresthesia	Any of the left, plus vomiting, involuntary defecation, or mission	Any of the left, plus organ bleeding	Any of the left
Respiratory Tract and Eyes	Sneezing, runny nose, nasal congestion, or ocular injection, itching, lacrimation	Any of the left, plus cough, wheezing, shortness of breath (e.g., less than 40% PEF drop, responding to an inhaled bronchodilator), itchy throat	Any of the left, plus shortness of breath (40% PEF drop, NOT responding to an inhaled bronchodilator), dyspnea, tightness, laryngeal or uvular edema	Any of the left, plus stridor, difficulty swallowing, hypoxia, cyanosis, asthma, respiratory failure,	Respiratory arrest
Cardiovascular System	-	Mild tachycardia (increase ≥20 bpm), and hypotension (drop SBP by ≥ 20 mmHg)	Evident tachycardia (increase ≥40 bpm), and hypotension (drop SBP by ≥ 40 mmHg)	Severe hypotension, dysrhythmia, bradycardia, shock, syncope, palpitations	Cardiovascular arrest
Nervous and Musculoskeletal Systems	Mild agitation, limited hyperactivity	Evident agitation, hyperactivity, weakness, headache	Exacerbated agitation, anxiety, dizziness, fainting, muscular cramps	"Lightheadedness", feeling of "pending doom", lack of muscular activity	Loss of consciousness
B) Warning signs for (Upcoming) Severe Anaphylaxis					
Time Interval between Allergen Exposure and Initial Symptoms	Many minutes	Few or many minutes	Immediately or a few minutes	Immediately or a few minutes	Immediately or a few minutes
Change of Time Interval compared to previous Event(s)	The same or longer	The same	The same or shorter	The same or shorter	The same or shorter
Cardio/Cerebro-Vascular Comorbidity, Asthma or Mastocytosis	-	-	Potential presence	Probable presence	Probable presence
Explanatory notes: These symptoms are not mandatory. The overall severity either is defined by the highest numerical value, i.e. most severe symptoms. Respiratory and cardiovascular symptoms are decisive in the assessment of anaphylaxis severity. Neurological symptoms (as an epiphenomenon of cardiovascular compromise) and cardio/cerebrovascular comorbidities are of less significant importance; however, a personal history of these diseases (or bronchial asthma) should be considered a risk factor for ineffective initial treatment, complications, and a warning signal to ask ICU personnel for assisting the treatment team. Prodromal symptoms and a short(er) time interval between the allergen exposure and symptoms' occurrence (when the respective cardiorespiratory symptoms are not present) should be an indicator for (temporary) observation of the subject in the red area of the emergency unit (including preparations for emergency measures). Hypotensive reactions lacking skin symptoms after exposure to culprit allergen(s) should be considered more severe than other reactions. Like cardiovascular diseases, headache in a subject with urticaria or angioedema should be regarded as a potential sign of arterial hypo/hypertension. Organ bleeding is a rare non-immune symptom of the anaphylactic reaction (mostly uterine) that may affect every inner organ (such as lungs, brain, etc.). NB Any medical personnel helping a patient with anaphylaxis should be alert for a rapid progression of the symptoms mentioned above and signs ready for quick counteraction!					

vasoconstriction circulatory exclusion, paleness, and cold extremities [27]. Experimental models have demonstrated that anaphylaxis is associated with hypothermia and reduced physical activity, and the last one inversely correlates with the release of serum mast cell protease [43,44]. In general, neurological and motor symptoms progress from warmth and agitation to anxiety or panic, cold extremities, paleness, and muscular cramps, and finally to physical inactivity, collapse, and loss of consciousness [17,18,21]. They are attributed to organ failure(s) due to inadequate blood pressure, influencing brain perfusion, consequently causing neurological symptoms [39,40]. Sampson has been the first author that included neurological symptoms in the classification of anaphylaxis severity. At the same time, Niggemann and Beyer claimed that such symptoms are subjective and less consistent with forming the basis for grading an immediate allergic reaction [15,17,19]. Being aware of this inconsistency, we have included neurological symptoms or the presence of cardio/cerebrovascular comorbidities: 1) to cope with the whole spectrum of symptoms, 2) because these factors are considered risk factors for severe anaphylaxis, ineffective treatment, and complications, therefore being an alarming signal for the requirement of ICU treatment [3,9,15,31,45]. The inclusion of neurological symptoms is based on the findings that resident cerebral mast cells can induce immediate reactions such as anaphylaxis and play a harmful role in cerebral microvasculature that promotes blood-brain barrier damage, brain edema, prolonged extravasation, ischemia, and hemorrhage [46]. Similar to cardiovascular pathologies, even an anaphylaxis-nonspecific neurological symptom like the headache in a subject with urticaria or angioedema should be considered a potential sign of arterial hypo/hypertension.

Consequently, medical personnel should be aware of a possible worsening situation. These facts point out that insufficient vascular circulation and the release of inflammatory mediators may affect physical activity, reduce the corporal temperature, and develop neurological deficiencies. Meanwhile, the personal history for cardio/neurovascular pathologies or neurological deficits can be risk factors for ineffective initial treatment, complications, and consequently, an alarming critical signal to ask ICU personnel for assisting the treatment team. These measures may include the use of cerebral protectors (edema reducing medicaments), sodium bicarbonate, restoring of peripheral circulation, etc.

(A)typical symptoms during anaphylaxis: Among organs where mast cell concentrations are the highest, angioedema and smooth muscle contraction can cause severe gastrointestinal or genitourinary symptoms, simulating an acute abdomen [7,24,47]. Although some authors have considered gastrointestinal symptoms in the historical classifications as overestimated, this approach included them because recognizing anaphylaxis symptoms and signs can sometimes be difficult for healthcare professionals [9,19,26]. Thus, in a blinded cross-sectional online survey of a random sample of emergency paramedical service personnel, only 3% recognized an atypical presentation of anaphylaxis in a patient with abdominal pain, hypotension, and no skin signs [9,48].

Unusual non-immunological manifestations may cause many difficulties recognizing anaphylactic symptoms and signs [40,49]. Organ hemorrhage such as uterine breakthrough bleeding can occur mainly in subjects with anaphylaxis to honeybee venom or during the respective immunotherapy [9,40,49,50]. Similar to gastrointestinal symptoms, this is attributed to venom-related interference with complement cleavage and bradykinin release [9,24,40,49]. These facts indicate that the specialized personnel should be aware of more minor typical symptoms during anaphylaxis to start the respective treatment at the appropriate time and avoid potential complications or critical situations.

Latency interval as a risk factor for severe anaphylaxis: Finally, the proposed instrument includes both the time interval between exposure to the culprit allergen and symptom occurrence and includes if the clinical signs have occurred in a shorter time interval than the previous episodes. These suggestions agree with the findings of Chapsa et al. [31] and Fehr et al. [51] they observed an association between severe systemic reactions to Hymenoptera venom and a short latency time or the absence of skin symptoms [31,51]. On average, the faster the allergic reaction occurred after the sting, the more severe it was. Consequently, the immediate occurrence of prodromal symptoms (such as tingling of palms or soles, a feeling of the warmth, or an unexplainable agitation) or the reduction of interval between the allergen exposure and initial occurrence of minor manifestations (when the cardiorespiratory symptoms are absent) in a subject with a positive history for immediate allergic reaction(s) can be used as a red flag. Such a patient should be observed in the red area of the emergency unit, etc. (including preparation for emergency measures), because the clinical situation may abruptly worsen. This opinion agrees with the finding that scoring severity of an anaphylactic reaction to exposure is complex due to the general nature of anaphylaxis (progression, timing, and interaction of symptoms), circumstantial challenges (terminated after the first clear objective signs), and treatment (immediately after that, hampering progression and overall severity) [15].

The precautionary preparation of emergency treatment (such as epinephrine) in an allergic patient with the immediate occurrence of distal paresthesia (tingling of palms or soles with or without classical skin manifestations) after exposure to the culprit allergen could be justified (and vindicated). There is general agreement that prompt initial treatment is essential in anaphylaxis. Even a few minutes' delays or suboptimal doses of epinephrine during the initial treatment may lead to hypoxic-ischemic encephalopathy or death due to sudden development of laryngeal edema or severe arterial hypotension [1,9,26,52]. Demonstration of the time-dependent and concentration-dependent pharmacologic effects of epinephrine in experimental studies also reinforces our suggestion [9,52]. These data agree with the clinical observation that epinephrine is maximally adequate when injected promptly in anaphylaxis [9]. Besides, Stoevesandt et al. [29]. have reported that cutaneous reactions during venom immunotherapy occurred exclusively after a longer median time interval when compared to moderate or severe reactions, suggesting that every prodromal symptom should be carefully considered [29]. These findings and arguments lead to the conclusion that early recognition of anaphylactic symptoms with a prompt institution of therapy (epinephrine) is central to a successful outcome [13].

Despite the objective limitations, these not well-defined criteria might be acceptable or usable because 1) in agreement with our suggestion, patients don't determine the latency interval precisely in a consistent proportion of cases; and 2) principally, they could help the specialized personnel to decide about the necessity of patient observation in the red area of the emergency unit and preparing of epinephrine for administration. In contrast, decisions about the principal therapeutic measures are based exclusively on the dynamism of the clinical criteria. Consequently, the inclusion of suggested anamnestic circumstances should not necessarily complicate the classification or limit its usefulness when patients were urgently admitted.

How could be validated this severity assessment tool?

The potential partial incorporation of this instrument in the future severity assessment systems may help allergists, emergency units, and ICU practitioners recognize supplemental clinical and anamnestic warning signals that account for potential disease worsening or complications. This recognizing can help them to avoid unnecessary fatal outcomes. The plan for the validation of our concepts could be based on certain cornerstones. The first point is comparing the needed medicaments and other measures in the case of severe cardiovascular implications: a) when skin symptoms occurred; and b) when skin symptoms not occurred. For example, our suggestion can be eligible if the quality and quantity of therapeutic measures necessary to avoid further complications show differences between the two cases (higher in the second group). The second point is identifying specific comorbidities like mastocytosis, neuro/cardiovascular disease, or bronchial asthma. In the case of positive history for such pathologies, the epidemiological findings of anaphylaxis outcome or the occurrence of critical disease complications should be compared between: a) cases of treatment according to usual protocols; and b) cases of assistance by ICU personnel according to their specific protocols, initiated immediately after patient admission. Our suggestion could be validated as eligible when the immediate treatment according to ICU protocols is more efficient in avoiding critical complications, worsened disease outcomes, or prolonged hospitalizations. The last point takes into account the latency interval between allergen exposure and symptoms' occurrence. In this case, patients with a repeated history of immediate allergic reactions (including anaphylaxis) should inform the emergency personal about the length of the time interval or if this interval is longer, the same length, or shorter than the previous episode. Then, the patient admitted after can ask symptoms' development to compare their severity to prior episodes when the latency interval was long(er) or short(er). The association of short(er) latency interval with a more severe reaction favors our suggestion. When the subject with history for anaphylactic reactions is admitted during latency interval or occurrence of prodromal signs, the comparison can be performed between: a) cases of standard observation protocol in the green area of the emergency unit; and b) cases of observation in the red area associated with the potential preparing of epinephrine injection. The higher frequency of delayed epinephrine administration and sudden disease worsening (because of the non-permanent observation among subjects under standard management protocol) could also be an additional argument in favor of proposed considerations.

Conclusions

Hopefully, testing reliability and validity for this approach in various settings and populations will allow eventual implementation in a standardized scoring system during clinical studies and routine practice. The potential incorporation of this instrument may help specialized caregivers recognize supplemental warning signals that account for potential disease worsening or complications and, therefore, help them avoid unnecessary fatal outcomes.

Acknowledgements

Mingomataj EÇ ideated the work and drafted the manuscript, Bakiri A contributed with literature collection and helpful discussions, and other authors also contributed with valuable discussions. All authors approved the manuscript content and agreed to the order of listed names.

References

1. Lieberman PL (2014) Recognition and first-line treatment of anaphylaxis. *Am J Med* 127: S6-S11. [Crossref]
2. Ballesteros-Martinez C, Mendez-Barbero N, Montalvo-Yuste A, et al. (2017) Endothelial regulator of calcineurin 1 promotes barrier integrity and modulates histamine-induced barrier dysfunction in anaphylaxis. *Front Immunol* 8: 1323. [Crossref]
3. Ring J, Behrendt H, de Weck A (2010) History and classification of anaphylaxis. *Chem Immunol Allergy* 95: 1-11. [Crossref]
4. Mueller HL (1959) Insect allergy. *Pediatr Clin North Am* 6: 917-952. [Crossref]
5. Ring J, Messmer K (1977) Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1: 466-469. [Crossref]
6. Clark S, Boggs KM, Balekian DS, Hasegawa K, Vo P, et al. (2018) Changes in emergency department concordance with guidelines for the management of stinging insect-induced anaphylaxis: 1999-2001 vs 2013-2015. Ann Allergy Asthma Immunol 2018; 120: 419-423. [Crossref]
7. Shmuel DL, Cortes Y (2013) Anaphylaxis in dogs and cats. *J Vet Emerg Crit Care (San Antonio)* 23: 377-394. [Crossref]
8. Hernandez L, Papalia S, Pujalte GG (2016) Anaphylaxis. *Prim Care* 43: 477-485.
9. Simons FE, Ardusso LR, Dimov V, Ebisawa M, El-Gamal YM, et al. (2013) World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol* 162: 193-204. [Crossref]
10. Ruiz Oropeza A, Lassen A, Halken S, Bindslev-Jensen C, Mortz CG (2017) Anaphylaxis in an emergency care setting: a one-year prospective study in children and adults. *Scand J Trauma Resusc Emerg Med* 25: 111. [Crossref]
11. Mingomataj E, Ohri D, Dhimitri V, Priftanji A, Qirko E, et al. (2003) Hymenoptera sting anaphylactic reactions in the Mediterranean population of Albania. *J Invest Allergy Clin Immunol* 13: 272-277. [Crossref]
12. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, et al. (2006) Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 117: 391-397. **[Crossref]**
13. Sheffer AL (2004) Anaphylaxis: clinical aspects. *Allergy Asthma Proc* 25: 31-32. [Crossref]
14. Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, et al. (2005) Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy* 60: 443-451. [Crossref]
15. Eller E, Muraro A, Dahl R, Mortz CG, Bindslev-Jensen C (2018) Assessing severity of anaphylaxis: a data-driven comparison of 23 instruments. *Clin Transl Allergy* 8: 29. [Crossref]
16. Ring J, Behrendt H (1999) Anaphylaxis and anaphylactoid reactions. Classification and pathophysiology. *Clin Rev Allergy Immunol* 17: 387-399. [Crossref]
17. Sampson HA (2003) Anaphylaxis and emergency treatment. *Pediatrics* 111: 1601-1608. [Crossref]
18. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G (2010) Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol* 125: 569-574, 574.e1-574.e7. [Crossref]
19. Niggemann B, Beyer K (2016) Time for a new grading system for allergic reactions? *Allergy* 71: 135-136. [Crossref]
20. Cox LS, Sanchez-Borges M, Lockey RF (2017) World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed? *J Allergy Clin Immunol Pract* 5: 58-62.e5. [Crossref]
21. Vetander M Helander D, Lindquist C, Hedlin G, Alfvén T, et al. (2011) Classification of anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. *Pediatr Allergy Immunol* 22: 369-373. [Crossref]
22. Mertes PM, Malinovsky JM, Jouffroy L, Working Group of the SFAR and SFA, Aberer W, et al. (2011) Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 21: 442-453. [Crossref]
23. Muraro A, Fernandez-Rivas M, Beyer K, Cardona V, Clark A, et al. (2018) The urgent need for a harmonized severity scoring system for acute allergic reactions. *Allergy* 73: 1792-1800. [Crossref]
24. Kaplan AP (2010) Kinins, airway obstruction, and anaphylaxis. *Chem Immunol Allergy* 95: 67-84. [Crossref]
25. Jerschow E, Lin RY, Scaperotti MM, McGinn AP (2014) Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. *J Allergy Clin Immunol* 134: 1318-1328.e7. [Crossref]
26. Fromer L (2016) Prevention of Anaphylaxis: The Role of the Epinephrine Auto-Injector. *Am J Med* 129: 1244-1250. [Crossref]
27. Triggiani M, Patella V, Staiano RI, Granata F, Marone G (2008) Allergy and the cardiovascular system. *Clin Exp Immunol* 153: S7-S11. [Crossref]
28. Yong SB, Chen HH, Huang JY, Wei JC (2018) Patients with urticaria are at a higher risk of anaphylaxis: A nationwide population-based retrospective cohort study in Taiwan. *J Dermatol* 45: 1088-1093. [Crossref]
29. Stoevesandt J, Hosp C, Kerstan A, Trautmann A (2014) Risk stratification of systemic allergic reactions during Hymenoptera venom immunotherapy buildup phase. *J Dtsch Dermatol Ges* 12: 244-256. [Crossref]
30. Manivannan V, Campbell RL, Bellolio MF, Stead LG, Li JT, et al. (2009) Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. *Ann Allergy Asthma Immunol* 103: 395-400. [Crossref]
31. Chapsa M, Roensch H, Langner M, Beissert S, Bauer A, et al. (2020) Predictors of severe anaphylaxis in Hymenoptera venom allergy: The importance of absence of urticaria and angioedema. *Ann Allergy Asthma Immunol* 125: 72-77. [Crossref]
32. Oropeza AR, Bindslev-Jensen C, Broesby-Olsen S, Kristensen T, Møller MB, et al. (2017) Patterns of anaphylaxis after diagnostic workup: A follow-up study of 226 patients with suspected anaphylaxis. *Allergy* 72: 1944-1952. [Crossref]
33. Kuda Y, Shibamoto T, Yang W, Zhang T, Tanida M, et al. (2017) Blockade of β2-adrenoceptor, rather than β1-adrenoceptor, deteriorates cardiac anaphylaxis in isolated blood-perfused rat hearts. *Cardiol J* 24: 403-408. [Crossref]
34. Lippert U (2017) Mastocytosis: Clinical aspects, diagnostics, therapy. *Hautarzt* 68: 67-75. [Crossref]
35. Richards JB, Wilcox SR (2014) Diagnosis and management of shock in the emergency department. *Emerg Med Pract* 16: 1-22; quiz 22-3. [Crossref]
36. Wacker DA, Winters ME (2014) Shock. *Emerg Med Clin North Am* 32: 747-758. [Crossref]
37. Lin RY, Schwartz LB, Curry A, Pesola GR, Knight RJ, et al. (2000) Histamine and tryptase levels in patients with acute allergic reactions: An emergency department-based study. *J Allergy Clin Immunol* 106: 65-71. [Crossref]
38. Kalesnikoff J, Galli SJ (2010) Anaphylaxis: mechanisms of mast cell activation. *Chem Immunol Allergy* 95: 45-66.
39. Taniguchi M, Higashi N, Ono E, Mita H, Akiyama K (2008) Hyperleukotrieneuria in patients with allergic and inflammatory disease. *Allergol Int* 57: 313-320. [Crossref]
40. Mingomataj EÇ, Bakiri AH, Ibranji A, Sturm GJ (2014) Unusual reactions to hymenoptera stings: what should we keep in mind? *Clin Rev Allergy Immunol* 47: 91-99. **[Crossref]**
41. Gouel-Chéron A, Neukirch C, Aubier B, Montravers P, Nicaise P, et al. Anaphylactic bronchospasm during general anesthesia is not related to asthma. *Allergy* 70: 453-456. [Crossref]
42. Nakamura Y, Hashiba Y, Endo J, Furuie M, Isozaki A, et al. (2015) Elevated exhaled nitric oxide in anaphylaxis with respiratory symptoms. *Allergol Int* 64: 359-363.

43. Manzano-Szalai K, Pali-Schöll I, Krishnamurthy D, Stremnitzer C, Flaschberger I, et al. (2016) Anaphylaxis Imaging: Non-Invasive Measurement of Surface Body Temperature and Physical Activity in Small Animals. *PLoS One* 11: e0150819. [Crossref]

44. Abril-Gil M, Garcia-Just A, Cambras T, Pérez-Cano FJ, Castellote C, et al. Motor activity as an unbiased variable to assess anaphylaxis in allergic rats. *Exp Biol Med (Maywood)* 240: 1373-1377. [Crossref]

45. Kim SM, Ko BS, Kim JY, Ook Ha S, Ahn S, et al. (2016) Clinical factors for developing shock in radiocontrast media induced anaphylaxis. *Shock* 45: 315-319. [Crossref]

46. Lindsberg PJ, Strbian D, Karjalainen-Lindsberg ML (2010) Mast cells as early responders in the regulation of acute blood-brain barrier changes after cerebral ischemia and hemorrhage. *J Cereb Blood Flow Metab* 30: 689-702. [Crossref]

47. Berin MC, Mayer L (2009) Immunophysiology of experimental food allergy. *Mucosal Immunol* 2: 24-32. [Crossref]

48. Jacobsen RC, Toy S, Bonham AJ, Salomone JA 3rd, Ruthstrom J, et al. (2012) Anaphylaxis knowledge among paramedics: results of a national survey. *Prehosp Emerg Care* 16: 527-534. [Crossref]

49. Mingomataj EC, Bakiri AH (2012) Episodic hemorrhage during honeybee venom anaphylaxis: potential mechanisms. *J Investig Allergol Clin Immunol* 22: 237-244. [Crossref]

50. Reisman RE (2005) Unusual reactions to insect stings. *Curr Opin Allergy Clin Immunol* 5: 355-358. [Crossref]

51. Fehr D, Micaletto S, Moehr T, Schmid-Grendelmeier P (2019) Risk factors for severe systemic sting reactions in wasp (Vespula spp.) and honeybee (Apis mellifera) venom allergic patients. *Clin Transl Allergy* 9: 54.

52. Kemp SF (2008) The post-anaphylaxis dilemma: how long is long enough to observe a patient after resolution of symptoms? *Curr Allergy Asthma Rep* 8: 45-48. [Crossref]