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A Proposal From The Montpellier World Health Organization Collaborating Centre For Better Management And Prevention Of Anaphylaxis

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ABREVIATIONS

AAI: adrenaline auto-injectors

BAT: basophil activation test

CAST: cellular allergen stimulation test

EAACI: European Academy of Allergology and Clinical Immunology

ICD: International Classification of Diseases

IgE: immunoglobulin E

WAO: World Allergy Organization

WHO: World Health Organization

ABSTRACT

Since the first description of anaphylaxis in 1902, its clinical importance as an emergency condition has been recognized worldwide. Anaphylaxis is a severe, potentially life-threatening systemic hypersensitivity reaction characterized by rapid onset and the potential to endanger life through respiratory or circulatory compromise. It is usually, although not always, associated with skin and mucosal changes. Although the academic/scientific communities have advocated to promote greater awareness and protocols for management of anaphylaxis based on best evidence, there are few efforts documenting feedback as to the success of these efforts. In this document, we review the key unmet needs related to the diagnosis and management of anaphylaxis, propose a public health initiative for prevention measures and a timetable action plan which intends to strengthen the collaboration among health professionals and especially primary care physicians dealing with anaphylaxis that can encourage enhanced quality of care of patients with anaphylaxis.

More than calling for harmonized action for best management of anaphylaxis to prevent undue morbidity and mortality, the Montpellier World Health Organization Collaborating Centre here proposes an action plan as a baseline for a global initiative against anaphylaxis. We strongly believe these collaborative efforts are a strong public health and societal priority that is consistent with the overarching goals of providing optimal care of allergic patients and best practices of allergology.

KEY WORDS: anaphylaxis, classification, epidemiology, management, treatment, prevention;

adrenaline/epinephrine auto-injector

COPING WITH ANAPHYLAXIS

Anaphylaxis: a “118 years-old killing lady”

In the time capsule of research and clinical advances in the field of allergy, the years of 1902 and 1913 signify milestones in the history of our specialty; in 1902, Paul Portier and Charles Richet’s described the experimental production of aberrant immunity, named “anaphylactique”, and the Nobel Prize of Medicine and Physiology was subsequently awarded for this finding in 1913 (1). Our understanding of the underlying mechanisms of anaphylaxis has evolved dramatically since the first studies associating the physiological actions of histamine and the concept of histamine shock as the basis of anaphylaxis in 1910 by Henry H. Dale (2). Half a century later, Kimishige Ishizaka, Teruko Ishizaka, Gunnar Johansson and their teams demonstrated immunoglobulin E (IgE) as a distinct class of immunoglobulin involved in allergic reactions (3). While Richet believed that anaphylaxis was a “lack of protection”, it has become clear that an exaggerated immune reaction, involving IgE, was the underlying pathomechanism in allergic anaphylaxis, besides immune complex reactions. Non-immunologically mediated reactions leading to similar clinical symptomatology have been called “anaphylactoid” or “pseudoanaphylaxis”, are now called “non-immune anaphylaxis”.

In the late 1990s, the allergy nomenclature was revised by Johansson et al., under the aegis of the European Academy of Allergology and Clinical Immunology (EAACI). The published document (4) has gained substantial international recognition and has been reviewed and endorsed by the World Allergy Organization (WAO) (5). This nomenclature has been accepted widely and is currently used worldwide. It was proposed that “anaphylaxis” would be the umbrella term for an acute reaction defined as a severe, life-threatening generalized or systemic hypersensitivity reaction. The term “allergic anaphylaxis” is used to define a reaction mediated by immunological, such as IgE, IgG and immune-complex complement-related mechanisms. Anaphylactic reactions mediated by IgE antibodies were referred to as “IgE-mediated allergic anaphylaxis.” Meanwhile, anaphylaxis from a non-immunological cause should be referred to as “non-allergic anaphylaxis.” The terms “anaphylactoid” and “pseudoanaphylaxis” are no longer used.

In the International Consensus on Anaphylaxis, published in 2014 (6), it was pointed out that the correct term anaphylaxis would be preferred to anaphylactic shock since shock is not necessarily present in patients with anaphylaxis. The term anaphylaxis should also be used in preference to terms such as allergic reaction, acute allergic reaction, systemic allergic reaction, acute IgE-mediated reaction, anaphylactoid reaction or pseudo-anaphylaxis (6,7).

Epinephrine (adrenaline) is the first medication of choice for the treatment of anaphylaxis (8). It is a potentially life-saving non-selective adrenergic agonist that acts though vasoconstrictor effects, preventing airway mucosal edema and hypotension, that also exerts bronchodilator activity and has inotropic and chronotropic cardiac effects (9). Epinephrine was first discovered by Japanese chemists Jokichi Takamine and Keizo Uenaka in 1900, two years before the first description of anaphylaxis (10,11). The therapeutic potential of epinephrine was widely acknowledged, and it was used before the molecule's mechanism of action was fully appreciated. Manufacturers then began developing synthetic forms of epinephrine. It was first synthesized in 1904 (12). The discovery and purification of epinephrine provided not only long overdue relief from anaphylactic reactions, but also contributed to the beginning of our understanding of hormones and homeostasis. Adrenaline auto-injectors (AAIs) are commercially available in many devices, in doses suitable for most, but not all, adults and children. For instance, in France four commercial forms are available, but the commercial availability varies in different countries (8) (Figure E1).

Since then, our progress in achieving further understand of anaphylaxis has slowed such that David B.K. Golden observed: "Portier and Richet would turn in their graves to know that we are little more enlightened than a century ago on the real nature of anaphylaxis" (13).

Anaphylaxis: what did we achieve so far?

The awareness of anaphylaxis as a life-threatening medical condition and its incidence have been increasing among different specialities. In recent years, evidence indicates its incidence has been increasing (14). The reported increases probably reflect a true increase in the prevalence of allergic disease, but are also confounded by cumulative incidence of anaphylaxis, better awareness and recognition of anaphylaxis, and changes in anaphylaxis coding, in part due to modifications in the international classification of diseases.

Anaphylaxis is recognized as a severe, life-threatening systemic hypersensitivity reaction, characterized by rapid onset and the potential to endanger life through respiratory or circulatory compromise. It is associated in most cases with skin and mucosal symptoms (15-19). It may present with different combinations of symptoms, and early onset of mild cutaneous pruritus may rapidly progress to entail a life-threatening reaction. This multi-faceted condition can manifest at any age and any health professional may be faced with it. Difficulty recognizing anaphylaxis can lead to delayed treatment with epinephrine and increase the risk of untoward outcomes including death (20,21).

The incidence of anaphylaxis ranges from 1.5 to 7.9 per 100 000 person-years in European countries (22) and 1.6 to 5.1 per 100 000 person-years in United States (23). Epidemiological data are heterogeneous for a number of reasons. Most of epidemiological studies have addressed subpopulations or specific triggers, which does not provide a global view from a public health perspective that would lead to general recommendations for clinical practice.

Anaphylaxis is a recognized cause of death in all age groups, in both genders and regardless of the ethnicity. The rate of anaphylaxis-related mortality is less than 1 per million per year in most high-income countries (15-19). There are limited epidemiological data from middle and low-income countries. One of the recognized difficulties in establishing accurate anaphylaxis data in population-based studies is the misclassification of this condition under the World Health Organization (WHO) International Classification of Diseases (ICD), but this may change with implementation of the ICD-11, which includes a chapter focused on allergic and hypersensitivity conditions (24-27).

Recently, the definition of anaphylaxis by the WAO was reviewed, in order to capture not only severe cases (26), but also to align this effort with the anaphylaxis definition proposed in the WHO ICD-11: “Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes” (26-28). From the initial description of anaphylaxis as a clinical entity with acute onset of symptoms involving 2 or more organs or with the association with hypotension or upper respiratory commitment, its definition has evolved to a more mechanistic description based on precision medicine into phenotypes with underlying endotypes supported by diagnostic biomarkers (29). Clinical and basic research have been done since the initial description of anaphylaxis 118 years ago, which has advanced the field and provided insight into its pathogenesis and management. For example, IL-33 has been described as key cytokine involved in anaphylaxis (30), neutrophils have been described as potential cellular actors in defined types of anaphylaxis (31) and PAF has been described as a new mediator of anaphylaxis among many other basic discoveries (32) and the fact that chemotherapy and monoclonals have been described as the new most important drugs inducing anaphylaxis (33) . Also, mastocytosis, hereditary alpha tryptasemia and non clonal mast cell activation syndrome have been described as the essential clinical causes of anaphylaxis.

The WAO also reviewed the diagnostic criteria of anaphylaxis as follows (28) (Table E1).

Although the academic/scientific communities have made efforts to work on documents to advocate in favour of awareness and management (15-19,34-37), there are few publications documenting the populations’ feedback to the awareness efforts.

LESSONS FROM THE FIELD

Clinical vignette: "I can't breathe well!"

"I can't breathe well" was the chief complaint of a 14 year-old girl in 3 previous episodes of anaphylactic reactions during the winter of 2018-2019 – each of which occurred with exercise. In addition to dyspnea and cough, she presented with palpebral angioedema and rhinoconjunctivitis symptoms. All episodes occurred with consumption of food including wheat or wheat-containing items within the several hours prior to exercise. In all episodes, she required emergency department management, receiving anti-histamines, inhaled Beta2-agonists and systemic corticosteroids. No adrenaline was administered.

She developed asthma in childhood, and was treated with a Beta2 agonist inhaler to be used on an as needed basis. Skin testing demonstrated wheal/flare reactions to multiple inhalant allergens including house dust-mite, cat dander, Alternaria alternata and pollens (olive, plane and birch trees, cypress, ambrosia, grass). Despite being multi-sensitized, sublingual allergen immunotherapy with cypress pollen was started in October 2019 and was associated with improvement in respiratory symptoms. The patient had no total serum tryptase measured. Her medications included valproic acid for seizure disorder.

Food-dependent exercise-induced anaphylaxis was suspected based on the clinical history. Serum specific IgE (4.5 KU/l) to wheat was detected with total IgE 3000 KU/l, and food provocation test with wheat and subsequent exertion (Treadmill challenge) and 500mg of Aspirin did not provoke generalized reaction. Despite this, the patient was advised to avoid wheat consumption before exercise. She received a written action plan and prescription of AAI.

In January 2020, the patient had another episode of anaphylaxis at home, presenting with occular and axillary pruritus, abdominal pain, pharyngeal edema with cough, urticaria and respiratory distress. Her mother administered EAI (Emerade® 300 µg) and emergency medical services was called. She also received systemic corticosteroids. However, she was advised to avoid a second administration of AAI. Her reaction progressed such that she developed vomiting and hypotension (systolic AP 80mmHg) at the time of the arrival of emergency medical services. No tryptase was measured during the acute phase of the anaphylactic reaction. Since our Allergy Department was also contacted, we recommended obtaining serum tryptase in the emergency department. Tryptase level was 7.2 µg/L (baseline: 3.7 µg/L) taken 4 hours after the acute phase, supporting a diagnosis of anaphylaxis. No specific trigger or co-factor was identified.

We reviewed the patient's files in order to identify possible non-investigated food triggers. Based on this evaluation, skin prick tests to pine nuts and tomato were performed and were positive. Differential diagnoses such as vocal cord dysfunction and features of dysautonomia have been ruled out. The patient is undergoing further investigation to revise management recommendations and a provocation test is scheduled.

This case highlights the challenges we may face in identifying an etiology for anaphylaxis in practice, and care in emergency departments that may not be consistent with best evidence and recommendations in recent guidelines (35). An understanding of the emergency medical assistance service for this patient has been set up but a standardized procedure for anaphylaxis with the measure of total serum tryptase dosage would be desirable at the Emergency department. A key point is the mistaken advice of not administering a second dose of epinephrine in the face of progressively worsening symptoms. We take this case as an example to call for harmonized actions for improved diagnosis and management of anaphylaxis.

Anaphylaxis: unmet needs

Since anaphylaxis entails the potential for rapidly developing life-threatening respiratory and/or circulatory compromise, prompt management is imperative. Over the last decade, the allergy/immunology community has intensified its efforts to encourage recognition and appropriate management of patients with anaphylaxis. However, gaps in understanding and implementation of management recommendations persist due to many factors including lack of a point-of-care diagnostic test, limited understanding of which patient may progress to life-threatening cardiopulmonary involvement, limited availability and appropriate use of first-line medications. Key unmet needs are:

Lack of adoption of standardized treatment protocols

Although the number of publications on anaphylaxis has increased over the last decade, anaphylaxis is still not consistently recognized by health care professionals and the optimal management is still hampered by specific false medical beliefs. Difficulty in the recognition of anaphylaxis is, in part, due to the variability of diagnostic criteria, and complicated by the heterogeneity in recommendations made by different national and international guidelines. Rarity of the event, multiple differential diagnoses and false medical beliefs also play a role. These factors tend to perpetuate a delay in administration of appropriate treatments, increase the risk of

untoward outcomes from anaphylaxis, and encumber epidemiological studies of anaphylaxis since medical records are the basis of national and international registries.

Many countries and regions have national anaphylaxis guidelines such as in France (34), Europe (16), the USA (35), Australia (36) and Latin America (37). Recently, consistent efforts have been made to reach a broader harmonization between these guidelines (6), but it is still necessary to have a unified management system for the benefit of patients worldwide.

Development of reliable markers for risk of severe/near-fatal/fatal anaphylaxis

Limited comparable epidemiological studies or research to increase understanding and to develop diagnostic and predictive tests remain key unmet needs. Data can differ widely depending on the number of variables (38,39). The most widely discussed issues in the epidemiology of anaphylaxis over the last 10 years are: (I) regional variations in concepts and definitions, (II) whether prevalence or incidence is the best measure of the frequency of anaphylaxis in the general population, (III) whether the frequency of anaphylaxis is higher than previously thought, and (IV) whether the increasing incidence published is real or reflects different methodologies and definitions used.

The etiology and risk factors/ co-factors for anaphylaxis described in epidemiologic studies are not well characterized and may indeed be influenced by regional/national differences in allergen exposures and genetic markers. In general, the most frequent triggers of anaphylaxis are drugs, foods and insect venoms. The frequency varies with age. Currently, anaphylaxis phenotypes are defined by clinical presentation into type-I-like reactions, cytokine storm-like reactions, and mixed reactions. The endotypes underlying these phenotypes include IgE- and non-IgE-mediated mechanisms, cytokine release, mixed reactions, and direct activation of immune cells (29). However, further elucidation of specific underlying mechanisms of anaphylaxis is required in order to better characterize anaphylaxis phenotypes and endotypes, and decrease the number of cases labelled as idiopathic anaphylaxis.

Frequent lack of appropriate follow-up from emergency departments

Anaphylaxis can occur in every setting, and pre-hospital management plays a crucial role in influencing outcomes of anaphylaxis (40-42). Therefore, patients and their caregivers have to be well prepared for prompt treatment of anaphylaxis based on written emergency action plans (7). Physicians, nurses and/or technicians working in ambulances should also be aware of first-line anaphylaxis management protocols and align their actions accordingly.

Most cases of anaphylaxis are first seen by emergency department physicians or general practitioners. However, only about 50% of patients are referred to allergists for further investigation and/ or treatment. Recommendations for follow up and trigger avoidance at time of discharge from the emergency room are provided infrequently (39). These data highlight the need for optimizing and standardizing protocols for anaphylaxis management, and implementing effective education and training programs. Also there should be specific programs in medical schools, residencies and postgraduate training programs that include aspects of anaphylaxis and its management, as well as funding for the postgraduate education of specialists.

Development of a rapid point-of-care diagnostic test

Although knowledge has evolved in specific areas, such as in food allergy, standardized diagnostic procedures should be tailored to specific triggers, combination of manifestations and specific age groups. Although standardized diagnostic procedures have been published, validation of these clinical tests for all allergens does not exist and multi-center, multi-national studies are needed. Generally speaking, diagnosis of allergen sensitization is made using skin tests (foods, Hymenoptera venom, some drugs and aeroallergens), serum allergen-specific IgE (foods, Hymenoptera venom, some drugs and aeroallergens), and provocation tests (foods, drugs) (43). Other complementary tests, such as cellular allergen stimulation test (CAST) and basophil activation test (BAT) and molecular diagnostic testing, are available in a number of countries, mainly for research purposes (44-47).

Serum (or plasma) levels of total tryptase and mature tryptase measurements are recommended in the diagnostic evaluation of anaphylaxis. However, the first measurement of serum tryptase during the acute event is seldom performed, or in some areas of the world this marker is not even available to be performed.

Lack of availability, adherence and use of essential medicine for anaphylaxis

Pharmacological treatment of anaphylaxis, including epinephrine, $\beta 2$ adrenergics, antihistamines, corticosteroids, dopamine, glucagon, and oxygen are available in virtually all countries. However, AAIs are not always available in most of world countries. In countries in which AAIs are commercially available, national policies regarding the availability of AAI at public settings are required (schools, public transport and etc).

Though there is no contraindication to epinephrine in the treatment of anaphylaxis and intramuscular administration is recommended, subcutaneous and intravenous administration are in

use in 10 to 20% of cases (mainly during peri-operative anaphylaxis) and in many other cases epinephrine is not even administered (34). There is also a lack of consensus regarding how long a patient with anaphylaxis should be kept under observation at the healthcare setting after treatment and resolution of the acute phase, especially in view of the possibility of biphasic reactions. Recently, the Joint Task Force Practice parameter on anaphylaxis rated the recommendation of extended clinical observation in a setting capable of managing anaphylaxis (to detect a biphasic reaction) for patients with resolved severe anaphylaxis and/or those who need > 1 dose of epinephrine as having very low evidence (35). This low rate score for the recommendation may reflect the lack of comparable evidence-based data. The lack of research is directly due to the fleeting nature of anaphylaxis and the difficulty in doing studies in humans that could induce anaphylaxis.

ACTION PLAN FROM THE WHO COLLABORATING CENTER

Public health's core mission is prevention of injury or disease. Taking the concept of prevention levels and applying it to anaphylaxis (Table 1) facilitates understanding that the measures proposed as primary and secondary preventions are addressed mostly to asymptomatic conditions, in which the main concerns are identifying individuals or populations at risk (48).

Tertiary prevention strategies are the most familiar for physicians worldwide who are involved in clinical medicine. When applied to anaphylaxis, it is intended to reduce the risk of another reaction and/or manage it appropriately to avoid negative outcomes. Prevention of anaphylaxis depends primarily on optimal management of patient-related risk factors, strict avoidance of confirmed relevant allergens or triggers, and, where indicated, immunomodulation (e.g., Hymenoptera venom immunotherapy) (48).

In June 2018, the **WHO Collaborating Center (WHO CC) for the Scientific Classification of Allergic and Hypersensitivity Diseases** was established at the University Hospital of Montpellier, headed by Luciana Kase Tanno and Pascal Demoly (49). This designation is the result of recognition by WHO of all the efforts of the ALLERGY in ICD-11 initiative (24,25,27, 50,51) and is intended to provide academic, research and scientific support to WHO in the implementation, refinement and maintenance of the WHO-FIC (Family of International Classifications) in our areas of expertise. WHO CCs are institutions designated by the Director-General of the WHO and endorsed by the national minister of health to carry out activities in support of the WHO programmes, such as communicable diseases, nutrition, mental health, occupational health among others. Currently, there are 25 WHO CCs responsible for the WHO-FIC and the Montpellier WHO CC is the only one with expertise in

allergy and clinical immunology. The WHO is a recognized specialized agency of the United Nations concerned with international public health. Since the Montpellier WHO CC is aligned with WHO actions to support the community, tailored actions for quality of care of patients, such as management and prevention of anaphylaxis, are under this context.

As the only WHO Collaborating Center for classifications of allergic and hypersensitivity conditions, we intend to establish close collaboration with national bodies in order to implement actions for better patients' care, monitor and prevention, developments in research, and launch measures in order to reduce avoidable deaths. Also, we intend to extend these actions internationally with the support of the WHO-FIC, academic and scientific networks, the Joint Allergy Academies, stakeholders and patients' organizations. Our WHO CC will provide the means through which governmental and nongovernmental collaborating parties can combine their strengths to achieve focused objectives, avoiding wasting of energy and resources.

The WHO CC can facilitate bilateral dialogue with these bodies and foster easier communication with health organizations. Our aim is to use the action plan applied to anaphylaxis as a model, but we may also extend this to other allergic and hypersensitivity conditions in the coming period. Human and financial resources will be required and may be achieved via support from the abovementioned bodies, robust research projects and structured collaborations. We intend to take all the support to move on the proposed action plan. For that, structured collaborations are under development.

Promoting increased awareness of anaphylaxis will be a key step forward. This will require consistent and bilateral communication with general practitioners, emergency department providers, primary care physicians, pediatricians and specialists, as well as other health professionals.

In order to align international and national efforts for increasing awareness, collaborations must be forged among professionals dealing with anaphylaxis. For this reason we propose a timetable schedule in order to optimize the diagnosis and management of anaphylaxis (Figure 1). A prioritized agenda should encapsulate all these steps in the frame of a global initiative against anaphylaxis. Countries with different economic conditions have specific priorities and requirements. The proposed action plan should support countries with different needs.

More than calling for harmonized action for best management of anaphylaxis to prevent undue morbidity and mortality, we are proposing an action plan as a baseline for a global initiative against anaphylaxis. We strongly believe these collaborative efforts are a strong public health and

308 societal priority, that is consistent with the overarching goals of providing optimal care of allergic
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References

1. Portier P, Richet C. De l'action anaphylactique de certains venins. C R Séances Soc Biol 1902;54:170.

2. Dale HH, Laidlaw PP: The physiological action of beta-imidazolethylamine. J Physiol 1910;41:318-344.

3. Ishizaka K, Ishizaka T, Hornbrook MM. Physicochemical properties of reaginic antibody. Presence of a unique immunoglobulin as a carrier of reaginic activity. J Immunol 1966;97:75-85.

4. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al.; EAACI (the European Academy of Allergology and Cinical Immunology) nomenclature task force. A revised **nomenclature** for allergy. An **EAACI** position statement from the **EAACI nomenclature** task force. **Allergy** 2001 Sep;56(9):813-24.

5. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. **J Allergy Clin Immunol**. 2004 May;113(5):832-6.

6. Simons FER, Ardusso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) Anaphylaxis. World Allergy Organ J 2014; 30; 7: 9.
7. Kase Tanno L, Demoly P. Anaphylaxis and pseudoanaphylaxis. Revue de Médecine Int 39 (2018) A2-A4.

8. Tanno LK, Demoly P; Joint Allergy Academies. Action Plan to Reach the Global Availability of Adrenaline Auto-Injectors. J Investig Allergol Clin Immunol. 2018 Nov 13:0.

9. Tanno LK, FER Simons, Sanchez-Borges M, Cardona V, Moon HB, Calderon M, Sisul JC, Casale T, Demoly P. Applying Prevention Concepts to Anaphylaxis: A Call For Worldwide Availability Of Adrenaline Auto-Injectors. Clin Exp Allergy, 2017, in press.

10. Yamashima T (May 2003). "Jokichi Takamine (1854–1922), the samurai chemist, and his work on adrenalin". Journal of Medical Biography. **11** (2): 95–102.

11. Bennett MR (June 1999). "One hundred years of adrenaline: the discovery of autoreceptors". Clinical Autonomic Research. **9** (3): 145–59.

12. Arthur G. Epinephrine: a short story. Lancet Respir Med. 2015 May;3(5):350-1.
13. Golden DB. What is anaphylaxis? Curr Opin Allergy Clin Immunol. 2007 Aug;7(4):331-6.
14. Lieberman P. Recognition and first line treatment of anaphyhalxis. Am J Med 2014; 127: S6-S11

15. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A et al. 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 2006;117:391– 397.
16. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014;69:1026–1045.
17. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010; 126:477–480.
18. Simons FER, Ardusso LRF, Bilo` MB, et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J 2011; 4:13–37.
19. Brown SG, Mullins RJ, Gold MS. Anaphylaxis: diagnosis and management. Med J Aust 2006; 185:283–289.
20. Tanno LK, Alvarez-Perea A, Pouessel G. Therapeutic approach in anaphylaxis. Curr Opin Allergy Clin Immunol. 2019 Aug;19(4):393-401.
21. Alvarez-Perea A, Tanno LK, Baexa ML. How to manage anaphylaxis in primary care. Clin Transl Allergy. 2017 Dec 11;7:45.

22. Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, Roberts G, Worm M, Bilò MB, Cardona V, Dubois AEJ, Dunn Galvin A, Eigenmann P, Fernandez-Rivas M, Halken S, Lack G, Niggemann B, Santos AF, Vlieg-Boerstra BJ, Zolkipli ZQ & Sheikh A on behalf of the EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy 2013; 68: 1353–1361.
23. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in United States: an investigation into its epidemiology. Arch Intern Med. 2001 Jan 8;161(1):15-21.
24. Tanno LK, Calderon MA, Demoly P; on behalf the Joint Allergy Academies. New allergic and hypersensitivity conditions section in the International Classification of Diseases-11. Allergy Asthma Immunol Res 2016;8:383-8.

25. Tanno LK, Chalmers R, Bierrenbach AL, Simons FER, Molinari N, Annesi-Maesano et al. on behalf Joint Allergy Academies. Changing the history of anaphylaxis mortality statistics througth the World Health Organization's International Classification of Diseases (ICD)-11. J Allergy Clin Immunol. 2019 Sep;144(3):627-633.

26. World Health Organization, ICD-11 Beta Draft website. (cited, available: http://apps.who.int/classifications/icd11/browse/l-m/en January 2020).
27. Tanno LK, Chalmers R, Jacob R, Kostanjsek N, Bierrenbach AL, et al. Global Implementation of the World Health Organization's International Classification of Diseases (ICD)-11: The Allergic and Hypersensitivity Conditions Model. J Allergy Clin Immunol. 2020, in press.

28. Turner PJ, Worm M, Ansotegui IJ, El-Gamal Y, Rivas MF, Fineman S, et al.; WAO Anaphylaxis Committee. Time to revisit the definition and clinical criteria for anaphylaxis? World Allergy Organ J. 2019 Oct 31;12(10):100066.
29. Castells M. Diagnosis and management of anaphylaxis in precision medicine. J Allergy Clin Immunol. 2017 Aug;140(2):321-333.
30. Claire Galand, Juan Manuel Leyva-Castillo, Juhan Yoon, Alex Han, Margaret S. Lee, Andrew McKenzie, et al. IL-33 promotes food anaphylaxis in epicutaneously-sensitized mice by targeting mast cells. J Allergy Clin Immunol. 2016 Nov; 138(5): 1356–1366.
31. Francis A, Bosio E, Stone SF, Fatovich DM, Arendts G, Nagree Y, et al. Neutrophil activation during acute human anaphylaxis: analysis of MPO and sCD62L. Clin Exp Allergy. 2017 Mar;47(3):361-370.
32. Kasperska-Zajac A, Rogala B. Platelet function in anaphylaxis. J Investig Allergol Clin Immunol. 2006;16:1–4.
33. *Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis.* J Allergy Clin Immunol. 2017 Aug;140(2):335-348.

34. Gloaguen A, Cesareo E, Vaux J, Valdenaire G, Ganansia O, Renolleau S., et al. Management of Anaphylaxis in Emergency Medicine. French Society of Emergency Medicine (SFMU) Guidelines with the Contribution of French Allergology Society (SFA) and the French Speaking Group in Pediatric Intensive Care and Emergency (GFRUP), and the support of the French pediatric pneumology and allergology society (SP2A). Ann. Fr. Med. Urgence (2016) 6:342-364.
35. Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020 Apr;145(4):1082-1123.
36. Vale S, Netting MJ, Ford LS, Tyquin B, McWilliam V, Campbell DE. Anaphylaxis management in Australian schools: Review of guidelines and adrenaline autoinjector use. J Paediatr Child Health. 2019
37. Cardona V, Álvarez-Perea A, Ansotegui-Zubeldia IJ, Arias-Cruz A, Ivancevich JC, González-Díaz SN, et al. Clinical Practice Guide for **Anaphylaxis** in **Latin America** (Galaxia-Latam). Rev Alerg Mex. 2019;66 Suppl 2:1-39.
38. Tejedor Alonso MA, Moro Moro M, Múgica García M V. Epidemiology of anaphylaxis. Clin Exp Allergy 2015;**45**:1027–1039.

39. Tanno LK, Bierrenbach AL, Simons FER, Cardona V, Thong BY, Molinari N, et al.; on behalf the Joint Allergy Academies. Critical view of anaphylaxis epidemiology: open questions and new perspectives. Allergy Asthma Clin Immunol. 2018 Apr 4;14:12.

40. Pouessel G, Dumond P, Liabeuf V, Kase Tanno L, Deschildre A, Beaumont P, et al. Gaps in the management of food-induced anaphylaxis reactions at school. Pediatr Allergy Immunol. 2019 Nov;30(7):767-770.

41. Lejeune S, Deschildre A, Beaudouin E, Labreuche J, Meininger C, Lefort H, et al. Pre-hospital management of paediatric anaphylaxis by French Emergency Medicine physicians: Still to be improved. Clin Exp Allergy. 2019 Jul;49(7):1047-1050.

42. Harper NJ, Cook TM, Garcez T, Farmer L, Floss K, Marinho S, Torevell H, Warner A, Ferguson K, Hitchman J, Egner W. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). British journal of anaesthesia. 2018 Jul 1;121(1):159-71.

43. Tanno LK et al. Management of Anaphylaxis: the World Allergy Organization Survey Identifies Achievements and Remaining Challenges. World Allergy Organ J. 2020, in press

44. Sala-Cunill A, Björkqvist J, Senter R, Guilarte M, Cardona V, Labrador M et al. Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. J Allergy Clin Immunol 2015;**135**:1031-1043.e6.

45. Khodoun M V, Strait R, Armstrong L, Yanase N, Finkelman FD. Identification of markers that distinguish IgE- from IgG-mediated anaphylaxis. Proc Natl Acad Sci U S A 2011;**108**:12413–12418.

46. Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organ J. 2020 Feb 25;13(2):100080.

47. Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Gomez RM, Ebisawa M, et al. A WAO-ARIA-GA2LEN consensus document on molecular-based allergy diagnosis (PAMD@): Update 2020 World Allergy Organ J. 2020 2020 Mar 7;13(2):100091.

48. Tanno LK, Simons FER, Sanchez-Borges M, Cardona V, Moon HB, Calderon MA, Sisul JC, Muraro A, Casale T, Demoly P; Joint Allergy Academies. Applying prevention concepts to anaphylaxis: A call for worldwide availability of adrenaline auto-injectors. Clin Exp Allergy. 2017 Sep;47(9):1108-1114.

49. World Health Organization, Collaborating Centres list website. (cited, available: http://apps.who.int/whocc/Detail.aspx?cc_ref=FRA-133&designation_date1=1/6/2018&designation_date2=18/7/2018& December 2019)
50. Tanno LK, Ganem F, Demoly P, Toscano CM, Bierrenbach AL. Undernotification of anaphylaxis deaths in Brazil due to difficult coding under the ICD-10. Allergy 2012; 67: 783–789.
51. Tanno LK, Calderon MA, Goldberg BJ, Gayraud J, Bircher AJ, Casale T et al. Constructing a classification of hypersensitivity/allergic diseases for ICD-11 by crowdsourcing the allergist community. Allergy 2015; 70: 609-15.

Figure 1: Timetable action plan proposal for the optimization of diagnosis and management of anaphylaxis

Table 1: Prevention concepts from a public health perspective, applied to anaphylaxis and intervention actions (adapted from 35)

LEVELS OF PREVENTION	APPLYING PREVENTION CONCEPTS TO ANAPHYLAXIS	INTERVENTIONS AND ACTIONS APPLIED TO ANAPHYLAXIS
Primary Prevention	Primary prevention addressed to anaphylaxis would imply the identification of individuals or populations at risk in order to avoid sensitization. For this, specific risk factors should be identified in unsensitized individuals with no history of an anaphylactic reaction.	– Increase health professionals' awareness through education and continuing education programs (e.g., breastfeeding, latex avoidance, early food diversification for infants). – Support dissemination of accurate information to the public (e.g., EAACI Anaphylaxis campaign, WAO Allergy week). – Specific interventions with early introduction of specific foods in the infant diets (e.g., peanut). – Remove strong sensitizers from public places and workplace environments (e.g., remove powdered latex gloves to prevent occupational latex allergy/ anaphylaxis, remove OTC use of pholcodine to prevent neuromuscular blocking agent anaphylaxis). – Labelling industrial products – Availability of adrenaline auto-injectors in countries in which it is not available in the heath system – Availability of adrenaline auto-injectors in public settings (schools, public transport and etc..) – Strengthen standard international definitions, notification, classification and coding (e.g., International Classification of Diseases) to support monitoring morbidity and mortality

Secondary Prevention	Secondary prevention in the context of anaphylaxis includes sensitized individuals with no history of an anaphylactic reaction. The aim is to prevent the development of an allergic disorder in patients previously sensitized. Screening of the general population for sensitization is not recommended. Sensitization is common and does not imply the diagnosis of an allergic disease. Screening should be applied to individuals with known risk factors.	– Individualized screening in order to identify sensitized individuals and support specific measures (e.g., those with occupational latex sensitization). – Individualized indication of adrenaline auto-injectors – Increase health professionals' awareness through education and regular information programs. – Strengthen standard international definitions, notification, classification and coding (e.g., International Classification of Diseases) to support monitoring morbidity and mortality.
Tertiary Prevention	Tertiary prevention: This concept should be focused on patients who have experienced an anaphylactic reaction. After initial clinical presentation, it is intended to reduce the risk of another reaction and/or manage it appropriately and avoid negative outcomes.	– Complete allergological work-up to confirm triggers (inducers) and support specific immunomodulation (e.g., allergen immunotherapy for Hymenoptera venom anaphylaxis or full drug allergy work up as indicated) and provide a written documentation of the diagnosis and the confirmed triggers/agents. – Individualize patient's education and provide specific information: environmental or behavior modifications to reduce patient's exposure to allergens, provide a written anaphylaxis emergency action plan. Adrenaline auto-injectors (individualized indication) – Support accurate food allergen labelling to protect consumers. – Support the emergency training of health professionals to rapidly identify and manage anaphylaxis. – Correct notification of new cases (e.g., as new allergens arise,

		support large cohort analysis). – Increase health professionals' awareness through education and continuous information programs. – Strengthen standard international definitions, notification, classification and coding (e.g., International Classification of Diseases) to support monitoring morbidity and mortality.

OTC, over-the-counter

Figure E1: Adrenaline auto-injectors commercially available in France (2018) and their differences (8).

HOME/ PUBLIC SETTING	EMERGENCY TRANSPORT	EMERGENCY DEPARTMENT/ HOSPITAL/ PRIMARY CARE	SPECIALIST (ALLERGIST)

Strengthen standard international definitions, notification, classification and coding (e.g., International Classification of Diseases) to support monitoring morbidity and mortality.

Education of medical students, residents, nurses and other key health care personal should be key to any improvement in the recognition of anaphylaxis and its management

- Identification of symptoms
- Prompt treatment and call the emergency following the written anaphylaxis action plan
- Availability of adrenaline auto-injectors in public settings (schools, public transport and etc..)
- Support dissemination of accurate information to the public (*e.g.,* EAACI Anaphylaxis campaign, WAO Allergy week).
- Specific interventions with early introduction of specific foods in the infant diets (*e.g.,* peanut).
- Remove strong sensitizers from public places and workplace environments (*e.g.,* remove powdered latex gloves to prevent occupational latex allergy/ anaphylaxis, remove OTC use of pholcodine to prevent neuromuscular blocking agent anaphylaxis).
- Labelling industrial products
- Individualize patient's education and provide specific information: environmental or behavior modifications to reduce patient's exposure to allergens, provide a written anaphylaxis emergency action plan. Adrenaline auto-injectors (individualized indication)

- Identification of symptoms
- Prompt treatment and call the emergency following the written anaphylaxis action plan
- Availability of adrenaline and/or adrenaline auto-injectors
- First measure of total serum tryptase measure
- Support the emergency training of health professionals to rapidly identify and manage anaphylaxis.
- Increase health professionals' awareness through education and continuous information programs.

- Identification of symptoms
- Prompt treatment and call the emergency following the written anaphylaxis action plan
- Availability of adrenaline and/or adrenaline auto-injectors
- First measure of total serum tryptase (if the blood sample has not been collected previously and if among first 2 hours of the symptoms)
- Individualized indication of adrenaline auto-injectors and avoidance of potential elicitors
- Refer to the allergist for further investigation
- Support the emergency training of health professionals to rapidly identify and manage anaphylaxis.
- Increase health professionals' awareness through education and continuous information programs.
- Correct notification of new cases.

- <u>Individualized screening</u> in order to identify sensitized individuals and support specific measures (*e.g.,* those with occupational latex sensitization).
- Individualized indication of adrenaline auto-injectors
- Second measure of total serum tryptase
- Complete allergological work-up to confirm triggers (inducers) and support specific immunomodulation (*e.g.,* allergen immunotherapy for Hymenoptera venom anaphylaxis or full drug allergy work up as indicated) and provide a written documentation of the diagnosis and the confirmed triggers/agents.
- Individualize patient's education and provide specific information: environmental or behavior modifications to reduce patient's exposure to allergens, provide a written anaphylaxis emergency action plan. Adrenaline auto-injectors (individualized indication)
- Increase health professionals' awareness through education and continuous information programs.
- Correct notification of new cases (*e.g.,* as new allergens arise, support large cohort analysis).