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Global disparities in availability of epinephrine auto-injectors

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ABSTRACT

Background: Anaphylaxis is the most severe clinical presentation of acute systemic allergic reactions and can cause death. Given the prevalence of anaphylaxis within healthcare systems, it is a high priority public health issue. However, management of anaphylaxis – both acute and preventative – varies by region.

Methods: The World Allergy Organization (WAO) Anaphylaxis Committee and the WAO Junior Members Steering Group undertook a global online survey to evaluate local practice in the diagnosis and management of anaphylaxis across regions.

Results: Responses were received from WAO members in 66 countries. While intramuscular epinephrine (adrenaline) is first-line treatment for anaphylaxis, some countries continue to recommend alternative routes in contrast to guidelines. Epinephrine auto-injector (EAI) devices, prescribed to individuals at ongoing risk of anaphylaxis in the community setting, are **only available in 60% of countries surveyed**, mainly in high-income countries. Many countries in South America, Africa/Middle-East and Asian-Pacific regions do not have EAI available, or depend on individual importation. In countries where EAIs are commercially available, national policies regarding the availability of EAIs in public settings are limited to few countries (16%). There is no consensus regarding the time patients should be observed following emergency treatment of anaphylaxis.

Conclusion: This survey provides a global snapshot view of the current management of anaphylaxis, and highlights key unmet needs including the global availability of epinephrine for self-injection as a key component of anaphylaxis management.

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COPING WITH ANAPHYLAXIS

Anaphylaxis: a hypersensitivity which can be fatal

Since the term "anaphylaxis" was first coined by Charles Richet and Paul Portier,[1] recognition of anaphylaxis as a public health issue has become widespread. Anaphylaxis should be considered a chronic non-communicable condition. It is defined as a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in the airway, breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present,[2,3] requiring prompt identification and treatment.

Regardless of the aetiology or underlying mechanism, intramuscular epinephrine (adrenaline) remains the medication of first choice in the treatment of anaphylaxis. Individuals at ongoing risk of anaphylaxis in the community are ideally prescribed self-injectable epinephrine, preferably as an auto-injector device (EAI), for use in an emergency. Although considered an important public health problem in some countries, it is still not considered a priority in many others, particularly in low-middle income countries.[4]

Due to the variety of different, multi-dimensional clinical presentations, unpredictable risk of fatality, and sudden onset in any setting, the allergy community has designated anaphylaxis as a high priority public health problem. The World Allergy Organization (WAO) is a federation of 108 Member Societies, whose mission is to be a global resource and advocate in the field of allergy, asthma, and clinical immunology, advancing excellence in clinical care through education, research, and training as a worldwide alliance of allergy and clinical immunology societies.[5] Since risk of anaphylaxis has a significant impact in patients' lives, WAO considers the quality care of patients suffering from severe hypersensitivity diseases, including risk of anaphylaxis, as a priority.[5,6]

To inform steps to improve the recognition and management of anaphylaxis, the WAO Anaphylaxis Committee and the WAO Junior Members (JM) Steering Group undertook an international survey focused on the acute and post-acute management of anaphylaxis globally.

Surveying the allergy community

An online questionnaire was created and peer-reviewed by members of the WAO Anaphylaxis Committee and JM steering group. The protocol was then approved by the WAO Executive Committee and Board of Directors. The final version consisted of 21 questions covering how anaphylaxis is diagnosed and managed in different healthcare settings, including availability of essential drugs and national health policies (Annex 1).

We developed a web-based survey using SurveyMonkey®, in English, which was circulated to members for 9 weeks. Responses were anonymized. The survey was sent to WAO members, including, but not limited to, the representatives of the constituent national societies of WAO, having authority to vote on their behalf, and the WAO JMs, and was also shared though social media. Responses were received from 43 countries representing all regions of WAO member Societies: Africa/Middle-East, Asia-Pacific, Europe, Latin America, and North America (Table 1).

Allergy and Clinical Immunology was recognized as a full specialty (69.3%) or as a subspecialty (17.7%) in the majority of countries. (Table 1). The majority (80.6%) of national allergy societies/associations are recognized by local regulatory bodies or by the Health Ministry.

Around half (55%) of countries surveyed had their own national anaphylaxis guidelines. Most countries in Latin America do not have their own specific guideline, but used international guidelines such as the Latin American Practice Guide for Anaphylaxis,[7]

Global region (total NO responses)	Country (N responses)	National allergy society/ association recognized by local regulatory bodies/health ministry	Availability of national registry of anaphylaxis cases?	Most frequent route of epinephrine (adrenaline) administration during the acute anaphylaxis	How long the patient is kept after the treatment of acute anaphylaxis	Estimated % of anaphylactic patients refereed to the allergists by the EDs
NORTH AMERICA (4)	United States of America (4)	Yes: 100% No: 0 Don't know: 0	Yes: 0 No: 100%	IM: 100% IV infusion: 0 IV bolus: 0 No experience: 0	<4 h 25% 4–8 hrs: 0 8–12 hrs: 25% 12–24 hrs: 25% >24 hrs: 0 Depends: 25%	<10%: 0 10–40%: 50% 40–60%: 25% 60–80%: 25% >80%: 0
SOUTH AMERICA (18)	Argentina (2) Brazil (2) Chile (5) Cuba (1) Ecuador (2) El Salvador (1) Mexico (6) Peru (1) Uruguay (2) Venezuela (1)	Yes: 83% No: 11% Don't know: 6%	Yes: 0 No: 100%	IM: 78% IV infusion: 11% IV bolus: 6% No experience: 6%	<4 h: 0 4–8 hrs: 39% 8–12 hrs: 28% 12–24 hrs: 11% >24 hrs: 6% Depends: 17%	<10%: 17% 10–40%: 45% 40–60%: 17% 60–80%: 11% >80%: 11%
EUROPE (23)	Albania (1) Belgium (1) Bulgaria (2) Croatia (1) Czech Republic (2) France (1) Germany (1) Italy (2) Poland (1) Portugal (2) Romania (1) Serbia (2) Slovenia (1) Spain (3) Ukraine (1) United Kingdom (1)	Yes: 87% No: 4% Don't know: 9%	Yes: 17% No: 83%	IM (82.6) IV infusion (13) IV bolus (2.2) No experience (2.2)	<4 h: 0 4–8 hrs: 26% 8–12 hrs 13% 12–24 hrs: 17% >24 hrs: 9% Depends: 35%	<10%: 0 10–40%: 30% 40–60%: 30% 60–80%: 13% >80%: 26%

(continued)

Global region (total NO responses)	Country (N responses)	National allergy society/ association recognized by local regulatory bodies/health ministry	Availability of national registry of anaphylaxis cases?	Most frequent route of epinephrine (adrenaline) administration during the acute anaphylaxis	How long the patient is kept after the treatment of acute anaphylaxis	Estimated % of anaphylactic patients refereed to the allergists by the EDs
AFRICA /MIDDLE-EAST (10)	Armenia (2) Belarus (2) Egypt (1) Kenya (1) Morocco (1) Pakistan (2)	Yes: 70% No: 10% Don't know: 20%	Yes: 20% No: 80%	IM: 50% IV infusion: 40% IV bolus: 10% No experience: 0	<4 h: 20% 4–8 hrs: 10% 8–12 hrs: 0 12–24 hrs: 20% >24 hrs: 30% Depends: 20%	<10%: 10% 10–40%: 20% 40–60%: 30% 60–80%: 30% >80%: 10%
ASIA- PACIFIC (17)	Australia (1) India (3) Indonesia (1) Japan (1) Malaysia (1) Philippines (1) Democratic People's Republic of Korea (3) Russia Federation (3) Sri Lanka (1) Viet Nam (3)	Yes: 77% No: 6% Don't know: 18%	Yes: 18% No: 82%	IM: 77% IV infusion: 18% IV bolus: 6% No experience: 0	<4 h (5.9) 4–8 hrs (17.6) 8–12 hrs (17.6) 12–24 hrs (17.6) >24 hrs (29.4) Depends on the severity (11.7)	<10%: 29% 10–40%: 35% 40–60%: 6% 60–80%: 18% >80%: 12%

Table 1. (Continued) Participating members, response rates, demographic characteristics, and general characteristics regarding managment and record of anaphylaxis. *(ICON = international consensus, IM = intramuscular, IV = intravenous, EDs = emergency departments)*

the Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology (57.7%)[7] and/or the WAO Guidelines for the Assessment and Management of Anaphylaxis (44.5%).[6] Only a minority of countries had a national registry for reporting of anaphylaxis cases (11.3%).

Management of acute anaphylaxis and follow-up

Intramuscular injection was the preferred route of adrenaline administration (86%), but the intravenous route is still used in a minority of settings (Table 1). Although most respondents reported observation of patients following anaphylaxis in excess of 4 h, there was wide variation in this, with many commenting that observation was dependent on reaction severity. In addition, the estimated proportion of patients experiencing anaphylaxis in the community who are then seen in the Emergency department (ED) and/or referred to allergy services was widely variable. (Table 1).

Second- and third-line medications for the treatment of the acute phase of anaphylaxis are available in the majority of countries (Table 2). However, some drugs such as Glucagon and Theophylline are mentioned as not available. Table 2 also shows that avoidance of the trigger and referral to the allergist are mainly performed at the ED or primary care prior to discharge. In countries where EAIs are available, it is prescribed in all 3 situations: prior to reaction following risk assessment, in the ED setting and during follow-up in primary care. However, where EAI are not nationally available, injectable adrenaline + syringe and needle are made available by ED and primary care doctors.

Global availability of epinephrine auto-injectors (EAI)

Most countries in the South America, Africa/Middle-East and Asian-Pacific regions do not have EAIs available or depend on its importation (Fig. 1). From 15 countries in which EAIs are available through importation, only 40% have them available nationally to the general public (on prescription). In the remaining 60% of countries, special license arrangements on a "named-patient" importation is required.

North America, specifically the United States, has EAIs nationally manufactured, and Anapen®, Auvi-Q®, and Epipen® are the EAIs commercially available in the American market. In Europe, 43.5% of participants reported that AAIs are nationally manufactured and 47.8% mentioned that they are available by importation. The main AAIs available in Europe are: Anapen®, Emerade®, Epipen® (also called Fastjekt® in German-speaking countries, Luxembourg and Italy), and Jext®. By contrast, in Austria is sold as Epipen®.[8] Twenty five percent of the respondents do not prescribe EAIs from overall 125 responses, while 33.3% prescribe 2 AAIs, and a remaining 23.3% restrict the prescription to 1 device, and 18.3% mention that it is dependable of the severity. National policies to availability of AAIs in public settings such as schools, public transports and parks are limited to some European, North American, and Asian Pacific countries (Table 3).

LESSONS FROM THE INTERNATIONAL SURVEY

This survey provides a worldwide overview of the management of anaphylaxis, and builds on previous WAO surveys, the last of which was conducted in 2010.[7–9] Anaphylaxis is still underrecognized and under-treated, in part, due to variability in diagnostic criteria across different guidelines.[6,7,9,10] As a consequence, this can lead to delays in treatment which can increase the risk of severe outcomes including death. The updated 2020 Anaphylaxis Guidance recently published by the WAO Anaphylaxis Committee seeks to address this by proposing updated diagnostic criteria for anaphylaxis which have been accepted by 53 national and regional member societies of WAO.[2]

Emergency medicines which might be used for the treatment of anaphylaxis, including epinephrine (adrenaline), β2 adrenergic agonists, H1 antihistamines, corticosteroids, dopamine, glucagon, oxygen, and methylxanthines (eg, theophylline) were available in all the countries surveyed. Concerningly, although epinephrine is the first line treatment of anaphylaxis in all guidelines, H1 antihistamines and corticosteroids remain the most frequently used drugs to treat this condition.

MEDICATIONS USED IN THE EMERGENCY FOR ANAPHYLAXIS	Available, prescribed and used	Available, but not prescribed	Not available	Total
Adrenaline	88.7% 55	11.3% 7	0.0% 0	62
Beta 2 - mimetics	70.2% 40	26.3% 15	3.5% 2	57
Antihistamines	95.0% 58	4.9% 3	0.0% 0	61
Corticosteroids	95.7% 59	4.8% 3	0.0% 0	62
Dopamine	37.9% 22	60.3% 35	1.7% 1	58
Glucagon	31.0% 18	62.0% 36	6.9% 4	58
Oxygen	86.7% 52	11.6% 7	1.6% 1	60
Theophylline	33.3% 19	61.4% 35	5.3% 3	57

RECOMMENDATIONS FOLLOWING THE ANAPHYLACTIC REACTION	Already in the place prior to reaction	At the emergency department/primary care prior to discharge	In primary care during a follow-up visit	Nothing	Total
Avoidance of the trigger	31.1% 19	54.1% 33	11.5% 7	3.3% 2	61
Adrenaline auto-injectors	25.4% 15	23.7% 14	23.7% 14	27.1% 16	59
Adrenaline inhalator	1.9% 1	9.4% 5	5.66% 3	83.0% 44	53
Injectable adrenaline + syringe and needle	17.8% 10	32.1% 18	17.8% 10	32.1% 18	56
Antihistamines	36.0% 22	49.2% 30	9.8% 6	4.9% 3	61
Corticosteroids	38.3% 23	50.0% 30	6.7% 4	5.0% 3	60
Inhaled beta-adrenergics	24.1% 14	29.3% 17	20.7% 12	25.8% 15	58
Training in emergency management plan (including drug training)	20.7% 12	22.4% 13	29.3% 17	27.6% 16	58
Referral to allergy (or other) specialist	19.6% 12	50.8% 31	26.2% 16	3.3% 2	61
Specific immunotherapy	17.8% 10	3.6% 2	42.8% 24	35.7% 20	56

Table 2. Medications used in the emergency for anaphylaxis and recommendations following the anaphylactic reaction

The survey indicates that EAIs are available in **60% of countries where responses were received:** mainly in high-income countries.[9] However, a study in 2018 reported that EAIs are only available **in 32% of world countries, absent mainly in low- and middle-income countries**.[11] In some countries, EAIs are only available by importation and with high cost. This category includes Epipen in Europe. Epipen in many European countries costs 10 times less than in the United States, despite being imported. We highlight that importation on a national scale is different from importation by individuals, in which the cost is generally covered by the patient. In regions where EAIs are commercially available, national policies regarding their availability in public settings are limited to a minority of countries (16%). There are also variations in terms of the number of EAIs prescribed to an individual patient.

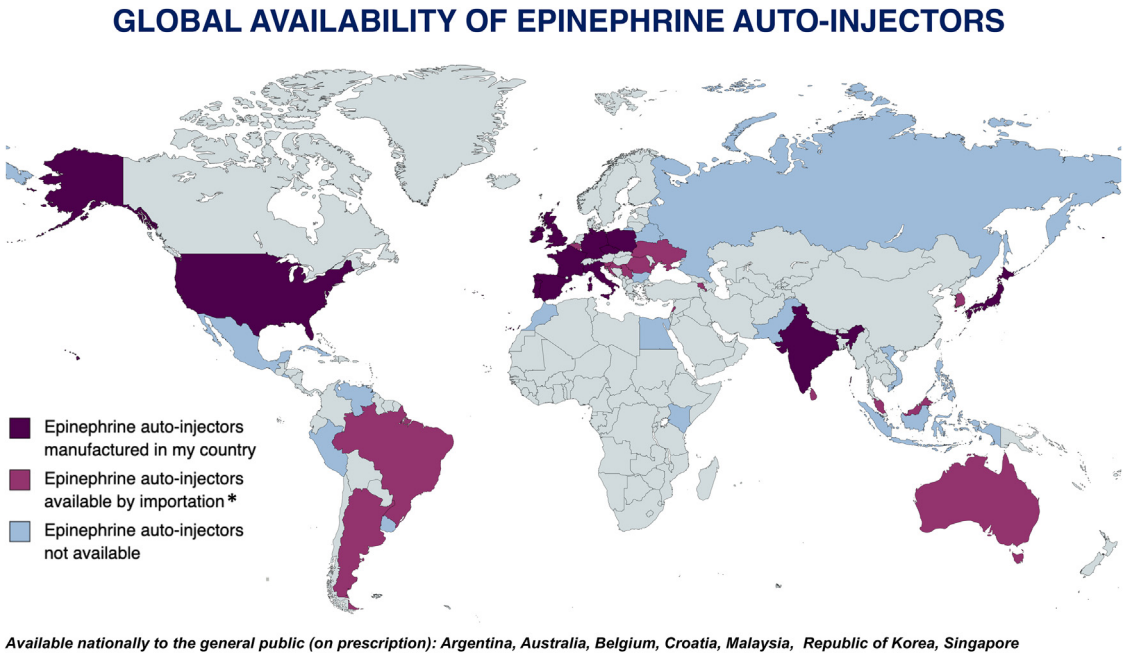

Fig. 1 Global availability of epinephrine auto-injectors according to the WAO anaphylaxis survey.

In some countries where EAIs are not available through official distribution networks (Fig. 1), they are available through distribution by special license arrangements, on a "named-patient" basis, or informally through the so-called "suitcase trade". This latter, unofficial source is unreliable because of the possibility of interruptions in the supply. Furthermore, shipping and storing EAIs under conditions outside the recommended temperature range is not recommended as this can lead to degradation of the adrenaline (epinephrine) content or even device malfunction. Where EAIs are not available, some patients and families will order them online from an international pharmacy or travel to another country to purchase them, although this clearly depends on the family's financial means.[11–14] Recent WAO Anaphylaxis guidance suggests the prescription of pre-filled syringes of adrenaline as an alternative to EAIs where these are not available.[6]

Although intramuscular epinephrine is recommended as the first line treatment for anaphylaxis, intravenous administration was estimated to be used preferentially in 10–20% cases in some countries. Adverse effects of epinephrine (adrenaline) via the intramuscular route are mild, well known and predictable such as tachycardia, headache, pallor, and tremor. Severe adverse effects (ventricular arrhythmias, pulmonary oedema, malignant hypertension, and intracranial haemorrhage) are rare but are more likely with the intravenous route of administration in the non-cardiac arrest setting, particularly bolus administration; dosing errors with intravenous use are also more common, increasing the risk of adverse events.[15–17] Our data show that in real life the time taken to act after an episode of anaphylaxis is extremely variable, depending on the health system of the countries in which the event occurs, as well as on the severity of the specific episode.

There is still a lack of consensus regarding how long an individual should be kept under observation in a medical facility following anaphylaxis. Currently, it still is an issue of debate.[18,19]

Most cases of anaphylaxis are first seen by emergency doctors or general practitioners.[20] However, only 50% of patients are referred to allergists for further investigation and management. These data highlight the need of optimizing referral pathways for patients at risk of anaphylaxis and implementing education and training programs.

Epidemiological data are key to tailor public health interventions and investments of health, such as the availability of EAIs. Limited comparable epidemiological studies or research to increase understanding and to develop diagnostic and predictive tests remain crucial unmet needs. Few

Global Region (NO responses)	National availability of epinephrine auto-injectors (%)	Epinephrine auto-injectors commercially available nationally (N) ***more than one response allowed*	Number of epinephrine auto-injectors prescribed to anaphylactic patient (%)	National policies to availability of epinephrine auto-injectors in public settings (%)
NORTH AMERICA (4)	Yes, nationally manufactured (100.0) Yes, by importation only (0.0) No (0.0)	Anapen® (1) Emerade® (0) Epipen® (4) Jext® (0) Auvi-Q® (4) Other (1)	1 (0.0) 2 (100.0) >2 (0.0) Depends on the severity of the reaction (0.0) Not prescribed (0.0)	Yes (50.0) No (25.0) Other (25.0)
SOUTH AMERICA (18)	Yes, nationally manufactured (0.0) Yes, by importation only (27.8) No (72.2)	Anapen® (2) Emerade® (1) Epipen® (5) Jext® (0) Auvi-Q® (1) Other (0)	1 (11.1) 2 (33.3) >2 (0.0) Depends on the severity of the reaction (0.0) Not prescribed (55.5)	Yes (0.0) No (100.0) Other (0.0)
EUROPE (23)	Yes, nationally manufactured (43.5) Yes, by importation only (47.8) No (8.7)	Anapen® (8) Emerade® (7) Epipen® (13) Jext® (8) Auvi-Q® (1) Other (2)	1 (34.8) 2 (34.8) >2 (0.0) Depends on the severity of the reaction (21.7) Not prescribed (8.7)	Yes (78.3) No (21.7) Other (0.0)
AFRICA/MIDDLE-EAST (10)	Yes, nationally manufactured (0.0) Yes, by importation only (10.0) No (90.0)	Anapen® (1) Emerade® (0) Epipen® (5) Jext® (0) Auvi-Q® (0) Other (0)	1 (0.0) 2 (0.0) >2 (0.0) Depends on the severity of the reaction (30.0) Not prescribed (70.0)	Yes (0.0) No (100.0) Other (0.0)

countries have national or regional anaphylaxis registries and data can differ widely depending on a variety of factors, such as patterns of drug/food consumption.[3] 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) misclassification and difficulties of coding anaphylaxis though international classification systems,[21,22] and (IV) whether the increasing incidence published is real or reflects different methodologies and definitions used. Large prospective population-based studies can increase our understanding of optimal patient management following the occurrence of anaphylaxis, for example recurrence rates. The implementation of anaphylaxis mortality and morbidity data through the ICD-11 may be a key instrument to achieve this.[21–26]

An important limitation of this survey is the different response rate by region and lack of responses from some countries. For example, the North America region has been represented by the United States only. We are aware that safe outcomes on an "anaphylaxis study" can be deducted only if a global survey, including the official National Position Statements, is performed. However, we considered the quality of these responses and considered them an estimate of real-life practice. We consider it unlikely that variations in response rate affected the overall data quality and analysis. Other factors, which may have influenced in the number of responses are: considerably high number of questions, limitation to access the online questionnaire, difficulties with the English language. Since the survey has been shared though social media it was not possible to access the response rate. Information of prevalence/incidence of anaphylaxis is limited in developing countries, which may be the reflex of under-notification, underdiagnosis and limited access to medical services.

This survey provides a global snapshot of the management of anaphylaxis and has flagged key unmet needs which must be addressed to improve the care of individuals at risk for anaphylaxis. WAO,[5] as an international federation, together with the Montpellier World Health Organization (WHO) Collaborating Centre,[27] are involved in all

Table 3. Worldwide view of availability and use of epinephrine auto-injectors

ASIA-PACIFIC (17)	Yes, nationally manufactured (17.6) Yes, by importation only (41.2) No (41.2)	Anapen® (1) Emerade® (1) Epipen® (11) Jext® (4) Auvi-Q® (1) Other (0)	1 (29.4) 2 (17.6)>2 (0.0) Depends on the severity of the reaction (11.8) Not prescribed (41.2)	Yes (23.5) No (76.5) Other (0.0)

actions to improve the quality of care of allergic patients, including the global availability of EAIs. These data are important to support future changes and harmonization, and to increase the quality of care received by individuals at risk of anaphylaxis patients.

Abbreviations

EAI: epinephrine auto-injector; BAT: Basophil activation test; ED: Emergency department; ICD: International Classification of Diseases; WAO: World Allergy Organization; WAO JMs: World Allergy Organization Junior Members; WHO: World Health Organization.

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Availability of data and materials

Raw data may be available after acceptance of the article and per request.

Authors' contributions

The first and last authors contributed to the construction of the document (designed the study, designed the questionnaire, analysed and interpreted the data, and wrote the manuscript). All the authors critically revised and approved the final version of the manuscript and agree to be accountable for all the aspects of the work.

Ethics approval

Not applicable. Responses for the survey were volunteer and data was anonymized.

Authors' consent for publication

All the authors consent for publication.

Declaration of competing interest

The authors declare that they do not have any conflict of interests related to the contents of this article.

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