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Latin American anaphylaxis registry

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ABSTRACT

Background: Recent data about clinical features, triggers and management of anaphylaxis in Latin America is lacking.

Objective: To provide updated and extended data on anaphylaxis in this region.

Method: An online questionnaire was used, with 67 allergy units involved from 12 Latin-American countries and Spain. Among data recorded, demographic information, clinical features, severity, triggering agents, and treatment were received.

Results: Eight hundred and seventeen anaphylactic reactions were recorded. No difference in severity, regardless of pre-existing allergy or asthma history was found. Drug induced anaphylaxis (DIA) was most frequent (40.6%), followed by food induced anaphylaxis (FIA) (32.9%) and venom induced anaphylaxis (VIA) (12%). FIA and VIA were more common in children-adolescents. Non-steroidal anti-inflammatory drugs (NSAIDs) and beta-lactam antibiotics (BLA) were the most frequent drugs involved. Milk (61.1% of FIA) and egg (15.4% of FIA) in children, and shellfish (25.5% of FIA), fresh fruits (14.2% of FIA), and fish (11.3% of FIA) in adults were the most common FIA triggers. Fire ants were the most frequent insect triggers, and they induced more severe reactions than triggers of FIA and DIA ($p < 0.0001$). Epinephrine was used in 43.8% of anaphylaxis episodes. After Emergency Department treatment, epinephrine was prescribed to 13% of patients.

Conclusions: Drugs (NSAIDs and BLA), foods (milk and egg in children and shellfish, fruits and fish in adults) and fire ants were the most common inducers of anaphylaxis. Epinephrine was used in less than half of the episodes emphasizing the urgent need to improve dissemination and implementation of anaphylaxis guidelines.

Keywords: Anaphylaxis, Latin America, Food hypersensitivity, Medication hypersensitivity, Insect venom hypersensitivity

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INTRODUCTION

Anaphylaxis is a severe, potentially life-threatening systemic, hypersensitivity reaction.[1] It typically occurs suddenly after systemic exposure to a triggering agent. Diagnostic criteria were proposed by Sampson et al.[2] in 2006, and subsequently adopted by the European Academy of Allergy and Clinical Immunology (EAACI),[3,4] the Latin American Society of Allergy, Asthma and Immunology (SLAAI)[5] and the World Allergy Organization (WAO).[6] Key information for diagnosis is the sudden onset after exposure to a trigger, with mucocutaneous (hives, angioedema), respiratory (dyspnea, wheezing), and or cardiovascular (hypotension, hypotonia, syncope) involvement.[2] Occasionally, mucocutaneous compromise is absent, and the sudden development of hypotension and/or dyspnea after exposure to a trigger are the only clues for diagnosis.[6] Circulatory collapse and airway obstruction can be fatal.

Specific nomenclature can be applied according to their most common inducers, such as drug induced anaphylaxis (DIA), food induced anaphylaxis (FIA), and venom induced anaphylaxis (VIA).[7-11] Foods are reportedly the most frequent triggers in children, whereas medications and insect stings are more common causes in adults.[7,8] Recent studies published in Latin-America (LA) regarding anaphylaxis epidemiology focused on specific triggers.[9-11] The aim of this study was to provide updated and extended data on the clinical presentation, severity, risk factors, triggers, cofactors, and treatment of anaphylaxis in LA and Spain.

METHODS

A cross-sectional, descriptive study to assess the characteristics of anaphylaxis in LA and Spain was conducted using an online questionnaire designed by the Anaphylaxis Interest Group of the SLAAI for this project. As Spain is a member of the Society, data from that country and LA were compared. A total of 67 allergy units from 12 LA countries and Spain participating in this registry, reported cases from July 2018 to December 2021 (Supplemental Table 1). Tertiary referral hospitals and/or university-based centers (n = 47), and multispecialty groups-based centers and private clinics (n = 20) participated.

The definition and severity rating for anaphylaxis was based on the 2006 guidelines by Sampson et al,[2] and severity rating criteria by Brown et al.[12] The definition of anaphylaxis and severity rating were included in the questionnaire survey form to ensure that all the reporters used the same criteria. Only reactions that occurred less than 24 months before the first visit date were included, to minimize recall bias.

The survey recorded demographic information, atopic status, clinical features, severity, time to symptom onset after trigger exposure, inciting agents, presence of comorbid conditions, treatment(s) received, and treatment response. Children/adolescents (0–17 years old), adults (18–59 years old), and elderly (60 years old or more) groups were compared. Confirmatory diagnostic assessment according to the patient's clinical presentation and availability of procedures at each facility (including skin prick and intradermal testing, provocation testing, and laboratory testing) was performed. Each questionnaire was included in the analysis after the diagnostic workup was completed.

Ethical considerations: Only procedures considered appropriate by the clinical investigator for the management of the anaphylactic reaction in question at each study site were performed on each patient. Questionnaires were completed by physicians retrospectively from the patient's medical records. This study was exempt and did not require an informed consent as all information was de-identified and all clinical information was reported anonymously.

Statistical analysis: OpenEpi software was used to analyze data.[13] Non-normally distributed quantitative variables were compared using the Mann-Whitney test and qualitative variables using the x2 test. All reported P values were based on 2-tailed tests; values less than 0.05 were considered statistically significant.

RESULTS

We analyzed 817 anaphylaxis reactions in 808 patients. Demographics are presented in Table 1. Anaphylaxis patients had a median age of 26

	Overall N (%)	Children-adol. N (%) (0–17 ys)	Adults N (%) (18–64 ys)	Elderly N (%) (65–84 ys)	p value		
					Adults/ children-adol.	Elderly/ children/adol.	Elderly/ adults
Patients n	808	334	433	41			
Age (y), median	26	5	37	69			
Sex, n (%)							
Male	353 (43.7)	205 (61.4)	135 (31.2)	13 (31.7)	<0.0001	<0.001	0.93 (ns)
Female	455 (56.3)	129 (38.6)	298 (68.8)	28 (68.3)			
Atopy, n (%)	497 (61.7)	200 (59.9)	278 (64.5)	16 (39)	0.22 (ns)	<0.05	<0.05
Rhinitis, n (%)	384 (47.6)	144 (43.1)	230 (53.4)	6 (14.6)	<0,01	<0.01	<0.0001
Asthma, n (%)	208 (25.8)	103 (30.8)	98 (22.7)	7 (17.1)	<0.05	0.06 (ns)	0.42 (ns)
Food allergy, n (%)	128 (15.9)	48 (14.4)	73 (16.9)	7 (17.1)	0.35 (ns)	0.63 (ns)	0.94 (ns)
Atopic dermatitis, n (%)	87 (10.8)	55 (16.5)	31 (7.2)	1 (2.4)	<0.0001	<0.01	0.26 (ns)
Hymenoptera venom allergy, n (%)	21 (2.6)	5 (1.5)	13 (3)	3 (7.3)	0.18	0.052 (ns)	0.19 (ns)
Latex allergy, n (%)	18 (2.2)	4 (1.2)	13 (3)	1 (2.4)	0.09 (ns)	0.53 (ns)	0.93 (ns)
Family history of allergy, n (%)	362 (44.9)	179 (53.6)	175 (40.6)	8 (19.5)	<0.001	<0.0001	<0.01

Table 1. Demographics of questionnaire subjects *Abbreviations: n = Number, y = years, adol: Adolescents.*

years (1 month–86 years old) with a female predominance in elderly and adults and a male predominance in children. There was no significant difference in severe anaphylaxis between genders in subjects 0–11 years old (female 34.8%; male 34.1%) or greater than 11 years old (female 34.6%; male 33.5%).

A high presence of atopy was found both in children/adolescents (59.9%) and adults (64.4%), but less so in elderly patients (39%) ($p < 0.05$). Atopic dermatitis was more frequent in children (16.5%) than in adults (7.2%, $p < 0.0001$) and elderly (2.4%, $p < 0.01$) subjects. FIA patients had more pre-existing atopic conditions (70.5%) than DIA patients (53.2%) ($p > 0.0001$), while 63.3% of the VIA patients had pre-existing allergic diseases. Interestingly, anaphylaxis was not more severe in asthma (severe reactions: asthma 32.7%, no asthma 34.9%) and allergic subjects (severe reactions: allergic 32.3%, non-allergic 37.7%). Table 2 shows anaphylaxis symptoms related to age, a history of previous anaphylaxis, and triggers. Most subjects exhibited cutaneous and respiratory involvement (94.1% and 79.4%, respectively). Specifically, urticaria (71%) and angioedema (67.7%) were the most common cutaneous symptoms and dyspnea (70.5%) the

	Overall	Children-adolescents n (%) (0–17 ys)	Adults n (%) (18–64 ys)	Elderly n (%) (65–84 ys)	Triggers n (%)				
					Food	Drugs	Insects	Others	Unknown
Anaphylactic reactions, n (%)	817	338 (41.4)	436 (53.4)	43 (5.3)	269 (32.9)	332 (40.6)	98 (12)	67 (8.2)	51 (6.3)
Cutaneous, n (%)	764 (93.5)	325 (96.2)	402 (92.2)	37 (86)	255 (94.8)	309 (93.1)	97 (99)	58 (86.6)	45 (88.2)
Respiratory, n (%)	649 (79.4)	258 (76.3)	357 (81.9)	34 (79.1)	198 (73.6)	272 (81.9)	78 (79.6)	58 (86.6)	46 (84.3)
Cardiovascular, n (%)	324 (39.7)	72 (21.3)	226 (51.8)	26 (60.5)	66 (24.5)	155 (46.7)	37 (37.8)	40 (59.7)	26 (51)
Gastrointestinal, n (%)	241 (29.5)	114 (33.7)	120 (27.5)	7 (16.3)	135 (50.2)	75 (22.6)	14 (14.3)	10 (14.9)	7 (13.7)
Previous anaphylactic reactions	198 (24.3)	45 (13.3)	147 (33.9)	6 (14)	90 (33.6)	56 (16.9)	16 (16.3)	22 (32.8)	14 (27.4)
Severity, n (%)									
Mild	87 (10.6)	38 (11.2)	46 (10.6)	3 (7)	28 (10.4)	37 (11.1)	9 (9.2)	8 (11.9)	5 (9.8)
Moderate	449 (55)	182 (53.8)	246 (56.4)	21 (48.9)	163 (60.6)	193 (58.1)	46 (46.9)	30 (44.8)	17 (33.3)
Severe	279 (34.1)	118 (34.9)	142 (32.6)	19 (44.2)	78 (29)	102 (30.7)	42 (42.9)	29 (43.3)	28 (54.9)
Fatal	3 (0.3)		3 (0.7)				2 (2)		1 (1)

Table 2. Symptoms, previous anaphylaxis and severity related to age and triggers *Abbreviations: n = number.*

most common respiratory symptoms. FIA induced more gastrointestinal (GI) symptoms (50.2%) and less cardiovascular (CV) involvement (24.5%) compared to DIA (GI: 22.6% $p < 0.0001$ and CV: 46.7%, $p < 0.05$, respectively) and VIA (GI: 14.3% $p < 0.0001$ and CV: 37.8% $p < 0.0001$, respectively). CV involvement was less prominent in children and adolescents compared to adults and elderly patients ($p < 0.000001$). (Table 2). Previous anaphylactic reactions were reported by 24.3% of subjects, and 58% of them reported more than 1 previous event. Previous episodes of anaphylaxis were more frequent in FIA (33.6%) compared to DIA (16.9%) and VIA (16.3%) ($p < 0.0001$) subjects. Anaphylaxis severity, summarized in Table 2 was not significantly different for any age group.

Triggers: Drugs were the most frequent triggers of anaphylaxis (40.6%), followed by foods (32.9%) and Hymenoptera venom (12%) (Tables 2 and 3, and Fig. 1). Specific triggers were not identified in 6.3% of subjects. DIA was more frequent in elderly and adult subjects ($p < 0.0000001$), while FIA and VIA were more common in children/adolescents ($p < 0.0001$). There was a shift from FIA and VIA to DIA at 10–12 years old children and older (Fig. 2).

DIA: Non-steroidal anti-inflammatory drugs (NSAIDs) and beta-lactam antibiotics (BLA) were the most frequent drugs triggering anaphylaxis in children-adolescents and adults, and beta-lactams were most common in the elderly ($p < 0.05$). Beta

Elicitor	Overall n (%)	<18 y n (%)	≧18–64 y n (%)	≧65 y n (%)
Drugs	332 (40.6)[a]	75 (9.1)[a]	227 (27.8)[a]	30 (3.7)[a]
NSAIDs	139 (41.9)	34 (45.3)	100 (44.1)	5 (16.7)
Metamizole 38 (11.4), ibuprofen 38 (11.4), diclofenac 23 (6.9), AAS 10 (3), ketorolac 6 (1.8), naproxen 5 (1.5), paracetamol 5 (1.5), and others 16 (4.8)				
β lactam antibiotics	87 (26.2)	22 (29.3)	53 (23.3)	12 (40)
Amoxicillin 38 (11.5), amoxicillin-clavulanic ac. 14 (4.2), cephalosporins 18 (5.5), and penicillin 17 (5.2)				
No-β lactam antibiotics	31 (9.3)	2 (2.7)	25 (11)	4 (13.3)
Quinolones 12 (3.6), trimethoprim-sulfamethoxazole 6 (1.8), minocycline 3 (0.9), others 10 (3)				
Anesthetics	11 (3.3)	2 (2.7)	6 (2.6)	2 (6.7)
Fentanyl 3 (0.9), lidocaine 3 (0.9), propofol 2 (0.6), succinylcholine 1 (0.3), Dexmedetomidine 1 (0.3) atracurium 1 (0.3)				
Contrasts	7 (2.1)	0	5 (2.2)	2 (6.7)
Iodine contrast media 6 (1.8) Patent blue 1 (0.3)				
Others	58 (25.6)	15 (20)	38 (16.7)	5 (16.7)
Food	269 (32.9)[a]	162 (19.8)[a]	102 (12.5)[a]	4 (0.5)[a]
Milk	104 (38.7)	99 (61.1)	4 (3.9)	1 (25)
Shellfish	34 (12.6)	7 (4.3)	27 (25.5)	0
Egg	25 (9.3)	25 (15.3)	0	0
Tree Nut	23 (8.6)	12 (7.4)	10 (9.8)	1 (25)
Fresh Fruits	19 (7.1)	4 (2.5)	15 (14.2)	0
Fish	14 (5.2)	2 (1.2)	12 (11.3)	0
Peanut	11 (4.1)	5 (3.1)	6 (5.7)	0
Mite containing flour	7 (2.6)	2 (1.2)	6 (5.7)	0

(continued)

Elicitor	Overall n (%)	<18 y n (%)	≧18-64 y n (%)	≧65 y n (%)
Soy	7 (2.6)	2 (1.2)	4 (3.9)	1 (25)
Wheat	5 (1.9)	2 (1.2)	3 (2.8)	0
Others	20 (7.4)	4 (2.4)	15 (14.7)	1 (25)
Insects n (%) rowhead	98 (12)[a]	59 (7.2)[a]	35 (4.3)[a]	4 (0.5)[a]
Fire ants	67 (68.4)	49 (83.1)	18 (46.2)	0
Bees	20 (20.4)	5 (8.5)	12 (34.3)	3 (75)
Wasps	3 (3.1)	1 (1.7)	2 (5.1)	0
Black ants	2 (2)	2 (3.4)	0	0
Others/ Unknown	11 (11.2)	2 (3.4)	3 (8.6)	1 (25)

Table 3. (Continued) Triggers of anaphylaxis, and their distribution (n, % within each group) in children and adolescents (aged <18 years-old), adults (aged ≥18-64 years-old) and elderly (aged ≥65 years old) *Abbreviations: n: Number, y = Years, NSAIDs: Non-Steroid Anti-inflammatory Drugs. [a]% total cases.*

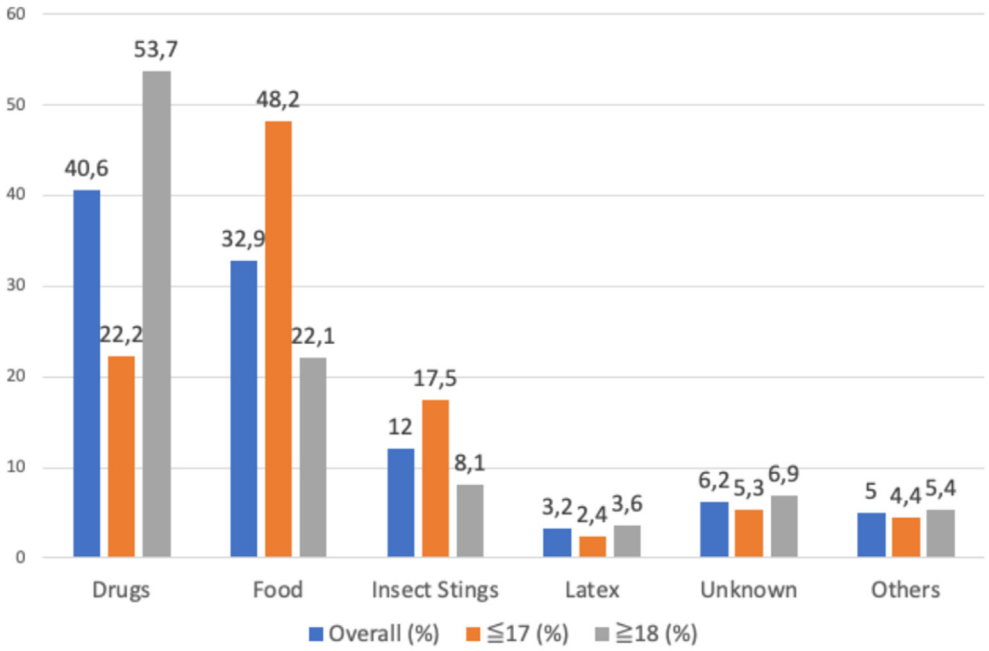

Fig. 1 Anaphylaxis triggers in children/adolescents and adults.

lactam antibiotics induced more severe reactions (44.8%) than NSAIDs (20.1%, OR 3.2 CI 1.7–5.8).

FIA: Milk (61.1% of FIA) and egg (15.4% of FIA) in children, and shellfish (25.5% of FIA), fresh fruits (14.2% of FIA), and fish (11.3% of FIA) in adults were the most frequent FIA inducers. Milk was the only trigger observed in infants 1–6 months (n = 12). For children younger than 2 years of age (n = 50), milk was the most common trigger (72%) followed by egg (18%) and peanuts (4.1%).

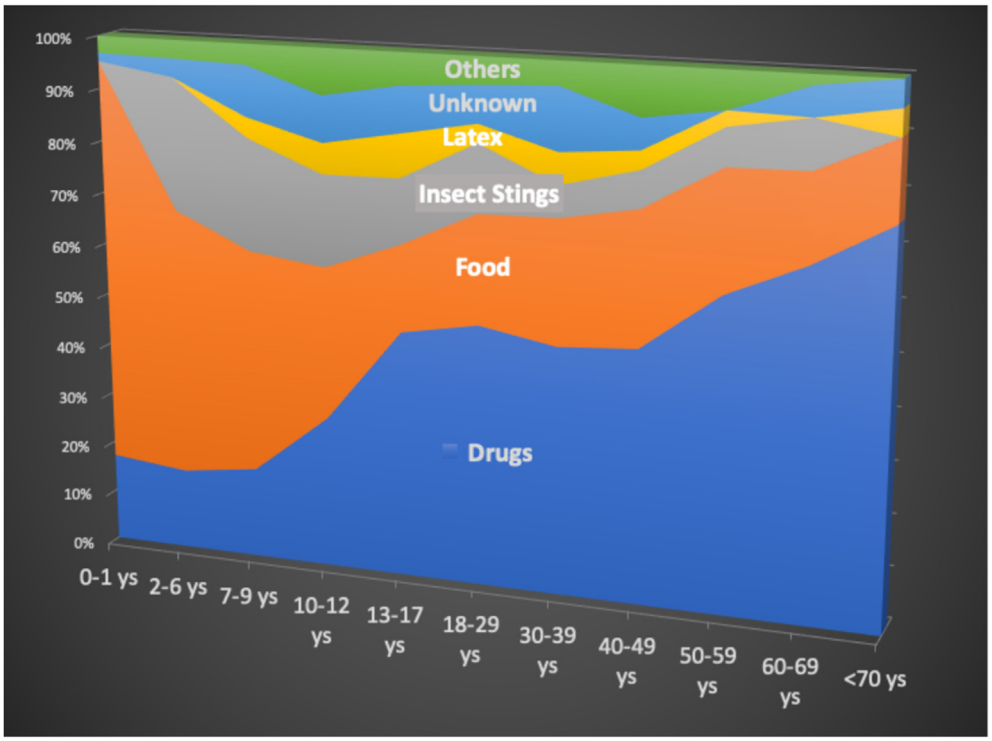

Fig. 2 Anaphylaxis triggers by age groups.

VIA: Fire ants were the most frequent insect trigger in children less than 2 years of age and the second most common trigger in children 2–9 years of age. Children 1–5 years of age had 26 fire ant, one black ant, and one bee triggered anaphylactic events, respectively. Hymenoptera venom was a more frequent trigger of VIA in older children/adolescents (14.3%) and adults/elders (38.5%), but in all groups, fire ants were the most common VIA trigger. Ninety-seven percent of fire ants induced anaphylaxis occurred in Argentina, Brazil, Paraguay and Mexico.

VIA, other less frequent triggers, and idiopathic anaphylaxis were associated with more severe reactions than FIA and DIA ($p < 0.0001$) (Table 2).

Triggers by age and age subgroups are illustrated in Figs. 1 and 2. In the group of children <18 years of age, foods were the main triggers, but in a subgroup analysis, drugs became the most frequent trigger in subjects 13–17 years of age and older (drugs n = 23, 47.9%; foods n = 8, 16.7%).

Infrequent triggers of anaphylaxis included latex (n = 26 cases), allergen immunotherapy (n = 7; n = 6 with dust mite and n = 1 with grass), vaccines (n = 5; one each for pneumococcal, rabies, pentavalent, influenza and COVID-19 BNT162b2 ARNm, Pfizer), monoclonal antibodies (n = 7; n = 4 rituximab and n = 1 each for tocilizumab, palivizumab, and adalimumab) and oral mite anaphylaxis ("pancake syndrome") (n = 7) were reported from the Dominican Republic (n = 5) and Peru (n = 2).

Most reactions (n = 683, 83.6%) occurred during the first hour after contact with the trigger; 374 (45.8%) occurred during the first 10 min, 219 (26.8%) from 11 to 30 min, and 90 (30%) between 31 and 60 min. Sixty percent of severe reactions occurred during the first 10 min, while only 38.2% of mild and moderate reactions occurred during this period ($P < 0.0000001$, OR 2.43). Previous allergic reactions with the same allergen occurred more frequently in FIA subjects (n = 110, 40.9%) compared to DIA (n = 88, 23.5%), and VIA (n = 22, 22.4%) ($p < 0.001$) subjects.

Cofactors were present in 278 (34%) reactions. NSAIDs were the most frequent cofactor (n = 103 reactions, 12.6%). In 6 cases, NSAIDs were associated with physical exercise as a cofactor. Infection was described in 81 cases (8%), stress in 57 cases (4.9%), and exercise with wheat ingestion, alcohol, stress, or on its own in 38 cases (4.7%). The menstrual period was reported in 13 cases. In many cases, more than one cofactor was present.

Fatalities: Although the study was not designed to report fatalities, 3 male patient deaths, 32, 38, and 42 years of age were reported. Two of these fatalities each had a history of 3 previous anaphylactic reactions after fire ant and Hymenoptera sting, respectively, and 1 with no allergic background and unknown trigger.

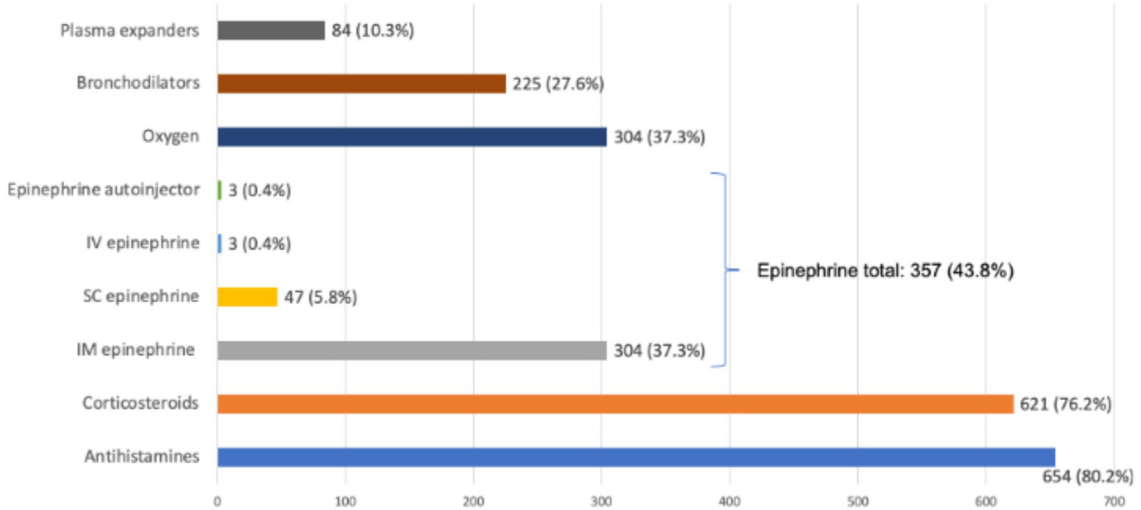

Fig. 3 Pharmacological treatment Abbreviations: IV: Intravenous, SC: Subcutaneous, IM: Intramuscular.

Treatment: Most reactions 556 (68.1%) were treated in the Emergency Department (ED); 130 patients (15.9%) were hospitalized; and 28 (3.4%) required admission to the Intensive Care Unit. Treatment at the physician's office was performed for 62 (7.6%) reactions; 53 (6.5%) cases were self-medicated, and 15 (1.8%) received no treatment. The pharmacological treatments received are depicted in Fig. 3. Antihistamines (n = 654; 80.2%) and corticosteroids (n = 621; 76.2%) were the most frequent drugs administered. Epinephrine was used to treat 357 (43.8%) reactions of which 304 (37.3%) reactions were treated using the intramuscular (IM) route. Post-treatment, 285 (35%) subjects improved within 1 h, 378 (46.4%) improved between 1 and 6 h, and 60 (7.4%) required more than 6 h. Biphasic anaphylaxis (BA) was reported by 8 (1%) subjects. No epinephrine was used in the treatment of this group and one reaction was rated as severe.

Post-discharge instructions included referral to an allergy service (79%), trigger avoidance (52.9%), written management action plans (25.5%), primary care referrals (10.8%), epinephrine autoinjectors (7.4%), alternative epinephrine injection formulations (5.6%), and no specific recommendations (4.3%). Serum tryptase was obtained in 4.5% of cases during the acute episode and 11.2% of cases during the allergy workup.

Cases from Spain (n = 45) and LA are compared in Table 4. Anaphylaxis in the pediatric group was more common in LA (42.6%) than Spain (15.5%). Spanish compared to LA cases had more frequent gastrointestinal involvement (44.4% vs 28.6%, $p < 0.05$) and fewer respiratory symptoms (66.7% vs 80.2%, $p < 0.05$). Cases of FIA were more frequently reported in Spain (57.8%) compared to LA (31.5%). Specifically, tree nuts and fruits were more common in Spain (26.9% and 19.2%, respectively) vs LA (6.2% and 5.3%, respectively), whereas milk-induced anaphylaxis was more frequent in LA (42.4%) compared to Spain (3.85%). Subjects were treated with IM epinephrine more frequently in Spain (47.7%) than LA (36.7%). Similarly, post-ED discharge epinephrine autoinjector prescription was more common for Spain (47.7%) than LA (36.7%) subjects.

DISCUSSION

The Latin American Anaphylaxis Registry, launched in 2018 by the SLAAI Anaphylaxis Committee is the largest and most detailed compilation of data on anaphylactic reactions in LA. As reported in previous studies, a female predominance in adults and elderly cases was found, while there was a male predominance for children.[10,11,14–18] Sex influence on the prevalence and severity of anaphylaxis in humans is not fully understood. Worm et al, using data from the European Registry, identified male sex as a predictor of anaphylaxis severity.[19] However, in our database, a difference in anaphylaxis severity between pre-puberal and post-puberal male and female patients was not found. The higher number of cases in the European Registry could account for this discrepancy with the LA registry.

Consistent with previous reports, an atopic background was less frequent in elderly patients[20] and atopic dermatitis was more frequent in children than adults and elderly patients.[7,16] In addition, FIA subjects had a pre-existing history of allergy or asthma more frequently than DIA subjects.[8] Also similar to previous studies, there was no difference in severity between cases with or without a pre-existing history of allergy or asthma.[10,16,19] Age is a well-known risk factor for severe anaphylaxis.[14,21] Although children and adolescents had less cardiovascular involvement than adults and the elderly, similar to the European Anaphylaxis Registry,[7,8,22] no significant difference in severity between groups was found which could be explained by a lower number of elderly cases in our study.

In this study, the most severe reactions began during the first 10 min after contact with the trigger, previously identified as a risk factor for severe anaphylaxis, strongly supporting the use of epinephrine autoinjectors.[23–25]

As in previous LA studies,[26,27] drugs were the most frequent anaphylaxis triggers in adults, followed by foods and insect venoms, while in children food was the most frequent trigger, followed by drugs and insect venoms. In contrast with our findings, VIA was the leading anaphylaxis trigger in the European Anaphylaxis Registry[22] and West Pomerania, Poland[28] and food was the

	Latin America (n%)	Spain (n%)	Statistical Significance
Anaphylaxis cases	772 (100)	45 (100)	
Children/adolescents	329 (42.6)	7 (15.5)	$p < 0.001$
Time to reaction 0–10 min	361 (44.2)	13 (28.9)	$p < 0.05$
Elicitors:			
DIA	320 (41.4)	12 (26.7)	NS
NSAIDs	137 (42.8[a])	2 (16.7[a])	NS
Beta Lactams	82 (25.6[a])	5 (41.7[a])	NS
FIA	243 (31.5)	26 (57.8)	$p < 0.001$
Milk	103 (42.4[a])	1 (3.8[a])	$p < 0.0001$
Nuts	15 (6.2[a])	7 (26.9[a])	$p < 0.01$
Fruits	13 (5.3[a])	5 (19.2[a])	$p < 0.05$
VIA	94 (12.2)	4 (8.9)	NS
Bees	17 (18.1[a])	3 (75[a])	$p < 0.05$
Treatment			
Intramuscular Epinephrine	283 (36.7)	21 (47.7)	$p < 0.0001$
ED Discharge			
Action Plan	188 (24.4)	20 (45.5)	$p < 0.01$
Epinephrine Autoinjector	48 (6.2)	20 (45.5)	$p < 0.0001$

Table 4. Latin America and Spain comparison *Abbreviations: n = Number, DIA = Drug-induced anaphylaxis, NSAIDs: Non-Steroid Anti-inflammatory Drugs, FIA= Food-induced anaphylaxis, VIA= Venom-induced anaphylaxis, ED = Emergency department. [a]% group.*

most frequent trigger in the United States,[29] Korea,[16] Portugal,[15] Qatar,[30] and Saudi Arabia.[31] These discrepancies may be related to different exposure frequencies, and heterogeneity between the populations studied.

Previous studies have shown, similar to this study, that NSAIDs were the most frequent drug triggers of anaphylaxis in LA[9–11,26,32] and other regions.[15,28,33–35] However, other studies, identified antibiotics as the more frequent trigger.[36–38] These findings may be explained by heterogeneity in the populations recruited. Almost one-third of DIA cases had a history of previous reactions with the same drug or a drug of the same group which is higher than previous LA reports[10,32] but lower than other studies in Brazil,[9,11] emphasizing the importance of educating physicians about taking a careful history regarding previous drug-induced hypersensitivity reactions as well as advising their patients about the consequences of self-medication and avoidance of the inciting drug or cross-reacting drugs responsible for the allergic reaction.

Food was the most frequent trigger in children, and second most common in adults. Cow's milk and hen's egg were most prevalent in preschoolers and school children up to 10–12 years old, consistent with studies from the United States, Korea, Portugal, and Europe.[7,15,16,30,39] Shellfish, fish, and fruits were common in teenagers and adults. Peanuts ranked seventh and tree nuts ranked fourth as anaphylaxis triggers in our study. Peanuts and tree nuts are major triggers of FIA in the United States, Middle East, Korea, and Europe,[1,30,39,40] but were less frequent in Latin America, with the exception of reports from Chile and Brazil[26,27,41,42] which

could potentially be explained by the lower consumption of these foods in these countries.

Francuzik et al[43] report using the European Registry data, found that VIA induced more CV involvement than other triggers. In the present study, VIA induced more cardiovascular involvement than food, and less than drugs. This difference may be explained by a greater number of triggers in the European Registry involved yellow-jackets and honey bees,[19,22] whereas fire ants, which are indigenous to LA, were the main VIA trigger in this study. In contrast to prior data both from LA[26,27] and other regions,[15,16,22] VIA in this study was more frequent in children/adolescents than in adults which may be explained by children having more exposure to these native insects than adults. Bee sting anaphylaxis was more frequent in adults, ranking second after fire ants. Different exposure patterns could explain the observed regional discrepancies. Most fire ant induced anaphylaxis occurred in Argentina, Brazil, Paraguay, and Mexico. These ants are native from Argentina, Brazil, Paraguay, and Uruguay, and have been introduced in Mexico from the United States.[44]

FIA cases had more recurrent reactions with the same allergen than DIA and VIA patients, similar to previous publications.[8,39,45] Interestingly, studies[46,47] have shown that NSAIDs and exercise can lower the anaphylaxis threshold, at least in wheat-induced anaphylaxis. Anaphylaxis cofactors were identified in one-third of cases in this study with NSAIDs being the most frequent and many episodes involving more than one cofactor.

Fatal anaphylaxis is uncommon, with an estimated fatality of approximately 0.5–1 per million persons/year.[48,49] Deaths due to foods (0.002–0.29 deaths per million persons/year) were rarer than Hymenoptera venom (0.02–0.61 deaths per million persons/year) or to drugs (0.004–0.56 deaths per million persons/year).[50] Three fatalities were reported in our registry, 2 of which were triggered by Hymenoptera venom. Both patients had 3 previous VIA episodes, however, mast cell activation syndromes were not investigated and basal serum tryptase or a peripheral blood KIT D816V mutation test was not determined for any of these cases.

Most patients were treated in the ED with antihistamines and corticosteroids. Only 43% received epinephrine, mostly by the IM route. The cornerstone of pharmacological treatment of anaphylaxis in all guidelines is IM epinephrine;[1–6] nevertheless, its use is suboptimal in most of the LA studies published to date[9–11,26,27,32] as well as in other regions of the world.[7,15,22] Moreover, for most anaphylaxis studies, antihistamines, and corticosteroids use was higher compared to epinephrine.[9–11,32] Gonzalez-Diaz et al[50] evaluated the knowledge of healthcare providers on anaphylaxis and found that the overall percentage of adequate answers (8 questions correct out of 12) was observed in only 28.7%. Epinephrine use as first-line indication was confirmed by 75% of the evaluated physicians, and only 26.7% of them answered that corticosteroids and antihistamines were a third-line therapy. Physicians with more than 30 years of experience and medical students achieved the best scores. Because most of these reactions are typically treated in the ED, implementation of anaphylaxis guidelines in the ED should be encouraged. Biphasic anaphylaxis (BA) was considered when anaphylaxis recurred 1–72 h (in most patients between 4 and 24 h) after improvement without new exposure to the trigger.[2,51] A recent study from the European Registry found these reactions occurred in 4.7% of anaphylaxis cases, mainly in severe reactions with multiorgan involvement.[51] Lee et al[52] in the United States identified BA in 4.1% of anaphylactic patients and delay in epinephrine administration (more than 1 h) as a risk factor for these reactions. Our study found 1% of BA, and none of these patients were treated with epinephrine.[53,54] Delay or absence of epinephrine use is a risk factor for BA.

Anaphylaxis guidelines[1–6] reinforce the recommendations for ED discharge. The World Allergy Organization (WAO) Anaphylaxis Guidance[6] states that "at the time of discharge from a health care setting, patients at risk of another episode of anaphylaxis, should be prescribed and taught about self-administration of epinephrine (adrenaline), and have a written personalized anaphylaxis emergency action plan". We found that only half of the patients were advised to avoid the anaphylaxis trigger, 1 of each 4 patients had a written management plan,

although only 13% received epinephrine prescription (autoinjectors only 7.4% or alternative formulations). The low autoinjectors prescription was probably related to the fact that these devices are not available in most Latin American countries, or are not affordable for most Latin American patients.

Serum tryptase levels can support anaphylaxis diagnosis after the initial treatment, and therefore baseline tryptase during the allergy workup is valuable in looking for mast cell disorders.[6] However, it was seldom reported in our study, probably related to its unavailability in most LA countries.

The strengths of this study are the use of a standardized clinical questionnaire, homogeneous anaphylaxis and severity definitions included in the form, and survey completion after allergy diagnostic procedures were done. Limitations included probable selection bias, as patients reported were studied by allergists and probably represent a fraction of the anaphylaxis cases in the communities studied. In a study from Banerji et al[55] in the United States, only 14% of the patients were followed up by an allergist in the subsequent year, after having a DIA treated in the ED or after hospitalization. The potential for population bias is probable, as treatment and reporting differences likely exist between sites. The present findings may not be generalizable as the population examined may not reproduce the true incidence or prevalence of anaphylaxis across communities in LA and Spain.

In summary, this registry-based study using a standardized questionnaire described the main features of anaphylaxis in countries from LA and Spain. Rapid developing reactions were usually more severe, emphasizing the importance of prescribing epinephrine (autoinjectors or other options) to all patients at risk for anaphylaxis. Drugs in adults and food in children were the most frequent triggers with NSAIDs and beta-lactam antibiotics being the most frequent drugs involved. Consistent with studies from the United States, Europe, and Korea, milk and egg were the most frequent FIA triggers in children.[7,14–16,39] In patients older than10-12 years, shellfish, fish, and fruits were the most common FIA triggers, and peanuts and tree nuts were less frequent in LA compared to other regions of the world. Fire ants were the most frequent VIA triggers in LA. Spain, compared with LA, had more FIA cases, mainly from tree nuts and fruits, more honey bee and no fire ant triggered VIA, as well as higher use of IM epinephrine and epinephrine autoinjectors prescribed post-ED treatment. However, epinephrine was used in the ED as acute treatment, and prescribed after treatment in less than half of anaphylaxis episodes both in Spain and LA, emphasizing the urgent need to improve dissemination and implementation of anaphylaxis guidelines.

Abbreviations

DIA, Drug induced anaphylaxis; FIA, Food induced anaphylaxis; VIA, Venom induced anaphylaxis; NSAIDs, Non-Steroid Anti-inflammatory; BLA, beta-lactam antibiotics; EAACI, European Academy of Allergy and Clinical; SLAAI, Latin American Society of Allergy, Asthma and Immunology; WAO, World Allergy Organization; LA, Latin-America; IM, intramuscular; ED, Emergency Department; BA, Biphasic anaphylaxis

Availability of data and materials

Data and materials are available at request from the corresponding author.

Author contributions

Dr Jares and Dr Cardona design the questionnaire. All authors contributed to the acquisition, analysis and interpretation of data. Dr Jares wrote the first draft of the manuscript, which was then reviewed, amended, and approved by all co-authors.

Ethics approval

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethics committee "Comité de ética e Investigación en Seres Humanos" (HCK-CEISH-19- 0058), Guayaquil, Ecuador.

Consent for publication

All authors consent the publication.

Declaration of competing interest

The authors report no competing interests. We confirm our manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

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Appendix A. Supplementary data

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