CLINICAL SCIENCE

Anaphylaxis in Latin America: a report of the online Latin American survey on anaphylaxis (OLASA)

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OBJECTIVES: The aims of the Online Latin American Survey of Anaphylaxis (OLASA) were to identify the main clinical manifestations, triggers, and treatments of severe allergic reactions in patients who were seen by allergists from July 2008 to June 2010 in 15 Latin American countries and Portugal (n = 634).

RESULTS: Of all patients, 68.5% were older than 18 years, 41.6% were male, and 65.4% experienced the allergic reaction at home. The etiologic agent was identified in 87.4% of cases and predominantly consisted of drugs (31.2%), foods (23.3%), and insect stings (14.9%). The main symptom categories observed during the acute episodes were cutaneous (94.0%) and respiratory (79.0%). The majority of patients (71.6%) were treated initially by a physician (office/emergency room) within the first hour after the reaction occurred (60.2%), and 43.5% recovered in the first hour after treatment. Most patients were treated in an emergency setting, but only 37.3% received parenteral epinephrine alone or associated with other medication. However, 80.5% and 70.2% were treated with corticosteroids or antihistamines (alone or in association), respectively. A total of 12.9% of the patients underwent reanimation maneuvers, and 15.2% were hospitalized. Only 5.8% of the patients returned to the emergency room after discharge, with 21.7% returning in the first 6 hours after initial treatment.

CONCLUSION: The main clinical manifestations of severe allergic reactions were cutaneous. The etiologic agents that were identified as causing these acute episodes differed according to age group. Following in order: drugs (31.2%), foods (23.3% and insect stings (14.9%) in adults with foods predominance in children. Treatment provided for acute anaphylactic reactions was not appropriate. It is necessary to improve educational programs in order to enhance the knowledge on this potentially fatal emergency.

KEYWORDS: Anaphylaxis; Drugs; Food; *Hymenoptera sp*; Epinephrine.

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INTRODUCTION

Anaphylaxis is defined as a serious, rapid onset, systemic allergic reaction that may cause death.[1-5] The diagnosis is based primarily on clinical history, and clinical criteria for accurate and early identification of anaphylaxis have recently been established.[1]

The lifetime prevalence of anaphylaxis from all triggers is estimated to range from 0.05% to 2.6%. Data on anaphylaxis prevalence and incidence are sparse, often inaccurate and underestimates the true incidence of anaphylaxis. The absence of a universal consensus on the definition of anaphylaxis, inadequate International Classification of Diseases (ICD) codes, and incorrect use of the terms 'prevalence' and 'incidence' in reports of anaphylaxis are reasons for the discrepancies in these findings.[5-14]

The triggers of anaphylaxis are represented by the following three general agents: foods, medications, and insect stings. These agents vary in prevalence according to the age of the studied population, the study design, and the geographic area. Foods are the most common causes of anaphylaxis in childhood, whereas medications and insect stings are more common causes in adults. Other, less common, causes in children and adults include latex,

immunotherapy-related reactions, exercise, cold and idiopathic causes.[5-14]

Although anaphylaxis is a severe acute reaction, fatalities due to anaphylaxis are rare. It is estimated that between 0.33 and 3 deaths per 1,000,000 people occur per year.[7,8,12-15] The prompt recognition of symptoms that potentially place patients at increased risk of severe anaphylaxis is mandatory for successful treatment and decrease death rate.[6] Concomitant diseases, such as asthma or other chronic respiratory diseases (especially those that are severe or uncontrolled), cardiovascular disease and mastocytosis are associated with the risk of life-threatening or fatal anaphylaxis. The use of β-blockers and angiotensin-converting enzyme inhibitors increase the severity of anaphylaxis, and β-blockers potentially make anaphylaxis more difficult to treat.[6]

Long-term treatment of anaphylaxis must be based on the identification of precipitating factors and the establishment of preventive measures to reduce the risk of a new anaphylactic episode. All guidelines mention that epinephrine as the only effective first aid treatment for anaphylaxis, but it is not usually administered soon enough after the onset of symptoms or after the exposure to an offending agent.[7,11,15-18]

Recently, Worm et al. proposed a pan-European registry of severe allergic reactions to obtain information about triggering allergens, aggravating factors, patient demographics and medical care.[19] It was proposed that the data of all registries in Europe be collected to allow physicians to promote knowledge on anaphylaxis.[19] Data on anaphylaxis in the Latin American region are scant. The objectives of the Online Latin American Survey of Anaphylaxis (OLASA) were to evaluate the main clinical manifestations, triggers, and treatment of patients with severe allergic reactions who were seen by allergists.

MATERIALS AND METHODS

A platform to collect information for OLASA (Encuesta/Denúncia de Anafilaxia en Iberoamérica online) was developed by the Latin American Society of Allergy, Asthma and Immunology (SLAAI). The data referred to patients who were seen by allergists and who presented with severe allergic reactions from July 2008 to June 2010. Attending allergists filled in a standardized OLASA questionnaire which was composed by 45 questions regarding the current episode and past episodes (triggering agent, clinical features, place of reaction, treatment received, place where reaction occurred, evolution of the current episode after treatment, frequency of episodes among others. This questionnaire, which was originally developed and validated in Portuguese,[20] was translated into Spanish and was available online at the SLAAI website.[21]

A total of 634 patients were registered from 15 countries: Venezuela (29.1%), Brazil (28.3%), Argentina (26.3%), Mexico (3.6%), Chile (2.4%), Colombia (2.2%), Uruguay (2.2%), Ecuador (2.1%), Cuba (1.3%), Portugal (1.3%), Nicaragua (0.06%), Bolivia (0.06%), Paraguay (0.05%), Peru (0.05%), Panama (0.01%), and the Dominican Republic (0.01%).

The results were presented as the simple frequency of positive answers relative to the total number of valid responses.

The study protocol was approved by the Ethics Committee of the Federal University of São Paulo, São Paulo, Brazil.

RESULTS

A total of 634 patients who were treated for systemic allergic reactions were enrolled in the study. The demographic characteristics showed a slight predominance of females (56.4%) with ages ranging from 1 to 97 years, stratified as follows: 8.0% were younger than 4 years old, 4.6% were 4-8 years old, 6.8% were 8-12 years old, 9.8% were 12-18 years old, 42% were 18-40 years old, and 26.5% were older than 40 years. An acute episode occurred at home in 65.4% of the cases. Table 1 shows the triggering agents assumed by patients for the most recent episode, with 87.4% identifying a trigger as drugs (31.2%), foods (23.3%) or insect stings (14.8%).

Table 2 shows the major clinical manifestations reported by patients. There was a significant predominance of cutaneous symptoms (pruritus and angioedema), followed by respiratory (dyspnea), cardiovascular (tachycardia), and gastrointestinal (nausea and dysphagia) symptoms.

Most patients (80.5%) had the current acute severe allergic epsiode treated in an emergency setting and the remaining at the place where the reaction occurred. The time to administration of emergency treatment was variable, with up to 15 minutes reported by 23.4% of patients, 15-30 minutes in 26.9%, 30-60 minutes in 19.9% and more than 60 minutes or unknown in 29.8%. With regard to symptom improvement, 43.5% of the patients observed improvement of their symptoms in the first hour after treatment, 45.1% observed improvement within six hours, and 11.2% reported improvement after six hours.

Isolated or associated medications that were used to treat acute episodes were recognized by 63.9% of the patients and included systemic corticosteroids (oral or injectable) in 80.5% of the patients, antihistamines (oral or injectable) in 70.2%, and epinephrine (subcutaneous or intramuscular) in 37.3%. A total of 12.9% of the patients required resuscitation while under hospital care.

After treatment, 67.3% of the patients were discharged from the emergency room as completely asymptomatic, 18.6% went home with medication, and 15.2% were hospitalized. Some patients (5.8%) needed to return to the hospital due to clinical impairment, which occurred at different times after discharge: 8.7% returned in the first hour, 13.0% returned between 1 and 6 hours, 45.7% returned between 6 and 24 hours, and 32.6% returned after 24 hours.

A history of previous acute severe allergic episodes was reported by 46.2% of the patients. Between 1 and 3 episodes were reported by 80.3%, 15.9% had 4-10 episodes, and 4.3% had more than 10 episodes. Time intervals between episodes was variable, at 15 to 29 days (7.5%), 30 to 60 days (8.7%), 2 to 6 months (6.2%), 6 to 12 months (15.2%) or more than a year (37.3%). Based on the severity of previous episodes, 19.7% reported more intense episodes, while 39.8% reported no change. Nevertheless, 32.6% of the patients required hospital assistance, and 5.0% were hospitalized.

When patients were discharged from the emergency room, only 19.5% received orientation on prevention of future attacks and to search for specialized treatment.

DISCUSSION

This is the first study to evaluate data from Latin American patients as registered by their attending allergists in an online survey. Patients were assisted in emergency rooms for severe

Table 1 - Main triggering agents for severe allergic reactions, according to the age of patients, registered in the Online Latin American Survey on Anaphylaxis.

Agents	Age (year)						
	1-4 N = 51 (%)	4-8 N = 29 (%)	8-12 N = 43 (%)	12-18 N = 62 (%)	18-40 N = 266 (%)	> 40 N = 168 (%)	Total N = 634 (%)
Drugs - total	**5 (9.8)**	**2 (6.9)**	**10 (23.3)**	**20 (31.7)**	**88 (33.1)**	**73 (43.5)**	**198 (31.2)**
NSAIDs	1 (1.9)	1 (3.4)	6 (14.0)	19 (30.6)	73 (27.4)	44 (26.2)	144 (22.7)
Antibiotics	4 (7.8)	1 (3.4)	4 (9.3)	-	12 (4.5)	15 (8.9)	36 (5.6)
Others	-	-	-	1 (1.6)	1 (0.3)	11 (6.5)	12 (1,9)
Local anesthetics	-	-	-	-	2 (0.7)	3 (1.8)	5 (0,8)
Food - total	**24 (47.1)**	**9 (31.0)**	**6 (14.0)**	**8 (12.9)**	**62 (23.3)**	**39 (23.2)**	**148 (23.3)**
Fish/seafood	1 (1.9)	3 (10.3)	1 (2.3)	4 (6.5)	37 (14.0)	22 (13.1)	68 (10.7)
Cow's milk/derivatives	14 (27.5)	2 (6.9)	1 (2.3)	-	1 (0.3)	2 (1.2)	20 (3.2)
Fruits	2 (3.9)	-	2 (4.7)	1 (1.6)	7 (2.6)	5 (2.9)	20 (3.2)
Wheat*	-	1 (3.4)	1 (2.3)	2 (3.2)	12 (4.5)	3 (1.8)	19 (92.9)
Peanuts	-	2 (6.9)	-	-	4 (1.5)	3 (1.8)	9 (1.4)
Eggs	6 (11.8)	-	-	-	-	1 (0.6)	7 (1.1)
Nuts	-	1 (3.4)	1 (2.3)	1 (1.6)	1 (0.3)	3 (1.8)	7 (1.1)
Manioc	-	-	2 (4.7)	-	-	1 (0.6)	3 (0.4)
Corn	1 (1.9)	-	-	2 (3.2)	-	-	3 (0.4)
Insects - total	**13 (25.5)**	**13 (44.8)**	**10 (23.3)**	**7 (11.3)**	**32 (12.0)**	**19 (11.3)**	**94 (14.8)**
Bees	2 (3.9)	4 (13.8)	6 (14.0)	7 (11.3)	16 (6.0)	12 (7.1)	47 (2.2)
Ants	9 (17.6)	8 (27.6)	1 (2.3)	-	10 (3.8)	1 (0.6)	29 (4.6)
Wasps	2 (3.9)	1 (3.4)	3 (7.0)	-	6 (2.3)	6 (3.6)	18 (2.8)
Immunotherapy	**-**	**1 (3.4)**	**4 (9.3)**	**4 (6.5)**	**4 (1.5)**	**2 (1.2)**	**15 (2.4)**
Latex	**-**	**-**	**-**	**2 (3.2)**	**6 (2.3)**	**1 (0.6)**	**9 (1.4)**
Exercise	**-**	**-**	**-**	**1 (1.6)**	**2 (0.7)**	**2 (1.2)**	**5 (0.8)**
Iodinated contrasts	**-**	**-**	**-**	**-**	**1 (0.3)**	**2 (1.2)**	**3 (0.4)**

*wheat contaminated with acari.
NSAIDs - non steroidal anti-inflammatory drugs.

acute allergic episodes by non-specialists who characterized the episodes as anaphylactic reactions. This condition could be a study limitation. However, all patients were evaluated by specialists and had the diagnoses confirmed before data were included in OLASA.[1-5]

Establishing prevalence and/or incidence rates was not the aim of this study. These indexes are usually based on data collected from Emergency Medical Services systems, emergency department visits, hospital admissions, visits to allergists, medical records obtained from resident populations of a specific area, and analysis of epinephrine auto-injector prescriptions. Each of these information sources has potential limitations because none of the them will cover 100% of cases.[7]

Almost 69% of the patients were older than 18 years, which may explain the higher prevalence of drugs, food and insect stings as triggers of anaphylactic reactions. However, as observed by other authors, the prevalence of particular triggers changes according to patient age. Foods, predominantly cow's milk, were more prevalent triggers among patients younger than 4, followed by insect stings and drugs (antibiotics). Among patients older than 8, the predominant causes were drugs (non steroidal anti-inflammatory agents and antibiotics) followed by foods (fish and seafood) and insect stings (bees and wasps) (Table 1). A retrospective review of 601 patients admitted to a reference service for evaluation of an acute episode of anaphylaxis showed the following trigger

Table 2 - Clinical manifestations during acute severe allergic reactions (% of each system involved).

Clinical manifestation	N	%
Cutaneous	**596**	**94.0**
Pruritus	323	54.2
Urticaria	81	13.4
Erythema	29	4.9
Angioedema		
Lips	305	52.0
Eyelids	118	19.8
Larynx	65	10.9
Face	28	4.7
Tongue	16	2.7
Glotis	12	2.0
Hands	11	1.8
Ears	8	0.7
Generalized	6	0.1
Testicle	3	0.05
Uvula	3	0.05
Respiratory system	**501**	**79.0**
Dyspnea	366	73.1
Suffocation	38	7.6
Cough	32	6.4
Hoarseness	29	5.8
Wheezing	26	5.2
Chest tightness	18	3.6
Rhinitis	18	3.6
Nasal congestion	14	2.8
Respiratory arrest	4	0.08
Stridor	4	0.08
Cardiovascular system	**254**	**40.1**
Palpitations	148	58.3
Dizziness	48	18.9
Syncope	33	13.0
Lipothymy	25	9.8
Gastrointestinal system	**193**	**30.4**
Nausea	71	36.8
Difficulty swallowing	62	32.1
Vomiting	24	12.4
Abdominal cramps	20	10.4
Diarrhea	11	5.7
Sphincter relaxation	2	1.0
Epigastralgia	2	1.0
Dysphagia	2	1.0

distribution: idiopathic (59%), food (22%) and medication (11%).[23] In our study, there was a lower prevalence of idiopathic anaphylaxis (17.8%), but the differences in age between sample populations could contribute to the contrasting observations. Food allergies are more common among children, whereas drug and hymenoptera venom allergies are more common among adults.[9-15,22]

Cutaneous symptoms predominated (94%) among patients registered in OLASA, most commonly pruritus (54.2%) and angioedema (52.0%). In a medical record review of patients with anaphylaxis from a private university-affiliated allergy clinic, 87% presented with urticaria and/or angioedema.[22] The next most common symptoms were respiratory (79%), mainly dyspnea (73.1%), which is similar to the level of 59% reported previously.[23] Cardiovascular symptoms were the third most commonly reported symptoms among patients (33% with syncope and dizziness), which is similar to the rate observed among our patients (40.1%), along with palpitation (58.3%). The clinical picture of patients in OLASA demonstrated that almost all patients presented cutaneous symptoms in addition to other organ involvement, in agreement with the definition of anaphylaxis.[1-4]

Although most reactions occurred at home, 60.2% of the patients were treated in the hospital, with 43.5% treated within the first hour of the reaction. However, few received appropriate treatment, considering that parenteral epinephrine is recommended by international guidelines as the only effective first aid treatment for anaphylaxis if it is administered soon after the onset of symptoms or after exposure to an offending trigger.[7,11,15,17,18,24,25] In this study, only 37.3% of the patients received epinephrine (subcutaneous or intramuscular) alone or in association with antihistamines (oral or parenteral) and/or systemic corticosteroids (oral or parenteral).

A questionnaire was sent to 52 Brazilian physicians working in emergency rooms to verify their medical skills in dealing with anaphylaxis and knowledge on refractory shock, biphasic reactions and management of patients on β-blockers. Adrenaline was the first choice in 63.4% of the cases, mostly via subcutaneous injections, although the site of injection was not indicated by 52% of the physicians. Corticosteroid injections ranked second in treatment prevalence. Glugacon was mentioned only once as a therapeutic alternative for patients on β-blockers. The biphasic anaphylactic reaction was not known by 75% of the physicians. This study highlights the educational deficiencies of physicians on duty in emergency rooms to manage anaphylaxis.[26]

After treatment, patients were kept in the emergency room for observation, and most were discharged without medication. Only 15.2% of the patients required hospitalization after emergency room treatment. This rate is in agreement with the average reported by Clark & Camargo, which found the rate of hospital admission after emergency room attendance to range from 3% to 41%.[11,13] An emerging concern is that admission rates vary across studies, mainly due to heterogeneous criteria for admission and the index applied. For example, the incidence of hospitalization has been reported to range from 5.6 per 100,000 to 11.05 per 100,000 hospital discharges.[27-29]

Biphasic anaphylaxis is the recurrence of symptoms within 72 hours with no further exposure to the allergen. It is estimated to occur in between 1% and 20% of cases, depending on the study,[30-32] and its management is similar to the treatment of anaphylaxis. In our study, we observed that 5.8% of patients could be characterized as having biphasic anaphylaxis because they returned to the emergency room due to symptoms after discharge, which happened in the first 6 hours for 21.7% of the patients.

Although 46% of the patients had a previous episode of anaphylaxis, which was considered less severe in 40.5% of the cases, only 19.5% had received orientation on the prevention of future episodes and referred to allergy clinics for treatment.

Our findings are alarming because even though anaphylaxis is a potentially fatal medical emergency, the therapeutic and educational approach toward it in Latin America is not appropriate. Knowledge of clinical manifestations and triggers are crucial to establish strategies for preventing and treating these episodes. Educational programs for general practitioners, pediatricians, and allied health professionals are necessary to enhance the knowledge of this emergency condition.

APPENDIX

The **Latin American Anaphylaxis Working Group** comprises: **Argentina:** Maria Laura Alassia, Dora Arab, Edgardo Azua, Gloria Bandin, Miriam Bercoff, Maria Eugenia Bessone, Pedro Hector Borthaburu, César Martin Bozzola, Adriana Monica Bracaccini, Raimundo Matias Camps, Silvana Paola Cardinali, Carlos Carignano, Gonzalo Chorzepa, Dario Colombaro, Mabel Cuello, Alicia De Falco, Monica Silvia De Gennaro, Juan Antonio Doglia, Pablo Fasano, Jorge Carlos Lujan Ferreyra, Roberto Festa, Fernando Luis Gambarte, Patricia Garnero, Mario Ceferino Gée, Hugo Ghiani, Nora Giovino, Maximiliano Gomez, Tomás Victoriano Herrero, Maria Del Carmen Imwinkelried, Edgardo Jares, Nestor Sergio Kahanovsky, Ivan Kriunis, Silvina Noemi Lisis de Wilson, Cecilia Lucini, Ana Maria Maldonado, Adriana Marcipar, Elsa Mindel, Hector Moisés, Juan Moura, Ernesto Muñoz, Julio Cesar Orellana, Roberto Jorge Pozo, German Dario Ramon, Daniela Sacerdote, Monica Sandra Sanabria, Wenceslao Sanchez de la Veja, Laura Sasia, Luis Sayago, Debora Seigelshifer, Roberto Gustavo Serrano, Marcelo Dante Strass, Olga Teresa Vazquez, Anahí Yáñez; **Bolivia:** Antonio Lopez, Alfredo Mendonza, Monica Sea; **Brazil:** Manoel Alves, Leandro Britto, Herberto José Chong Neto, Regina DiGesu, Luis Felipe Ensina, Fátima Fernandes, Mario Geller, Hermila Guedes, Fábio Kuschnir, Marta Machado, Alexandre Miyake, Charles Kirov Naspitz, Celso Eduardo Olivier, Hevertton Santos, Lucia Jasse Santos, Muller Tim, Vanessa Gonzaga Tava; **Chile:** Ana Maria Agar Muñoz, Ramón Canala-Echevarria, Enzo Espinola, Maria Antonieta Guzman, Maria Angelica Marinovic, Valentina Parada, Tamara Perez, Erna Ripoll, Paola Toche; **Colombia:** Ingrid Bissinger, Eduardo De Zubiria, Rodolfo Jaller Raad, Maria Victoria Morena, Carlos Serrano; **Cuba:** Mirta Alvarez, Osvaldo Batista Rojas, Raul Lázaro Castro, Raquel Garcia, Olimpio Rodriguez; **Dominican Republic:** Andres Socias; **Equator:** Ivan Cherrez Ojeda, Jose Luis Gonzalez Acuña, Rolendio Palacios, Ivan Tinoco, Rommel Valdivieso, Manuel Eduardo Viteri, Paul Wilches, John Haboud Zambrano, Edison Vicente Zapata Venegas; **Mexico:** Rodolfo Celio Murillo, Jose Refugio Enriquez Salazar, Mercedes Gomez, AryaYannel González-González, Luis Enrique Hernandez, Rosa Elena Huerta, Blanca Morfin, Gerardo Mortera, Adriana Elizabeth Peña Rued, Noel Rodriguez, Hector Manuel Ruiz Dias, Nora Hilda Segura, Hector Solorio, Jose Enrique Soria, Ana Maria Vegas, Tomás Velarde; **Nicaragua:** Guissele Urbina Palacios; **Panama:** Diva Almillategui; **Paraguay:** Jaime Alberto Guggiari Doutreleau, Manuel Ratti, Hector Ratti Sisa; **Peru:** Ricardo Farfan; **Portugal:** Angela Gaspar, Eva Gomes, Rodrigo Rodrigues-Alves; **Uruguay:** Graciela Castro, Grettel Morena, Juan Francisco Schuhl; **Venezuela:** Feres Abou Khair.

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