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## Anaphylaxis: An Analysis of Cases Evaluated at the Puerto Rico Medical Center Over a Ten-Year Period

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**Objective.** To examine the clinical characteristics of patients with anaphylactic reactions evaluated at the Puerto Rico Medical Center over a ten year period.

**Background.** Anaphylaxis, an immunologic reaction classically initiated by the combination of an antigen and a mast cell fixed antibody (usually IgE), still carries a fatality rate of 500 to 1000 cases per year in the United States. It constitutes a medical emergency that needs to be identified promptly in order to install appropriate treatment. No studies of this condition have been conducted in Puerto Rico, specifically to assess the clinical presentation, main causes and outcome.

**Methods.** Eighty-three records of patients with a diagnosis of anaphylaxis were screened by retrospective and concurrent analysis. Of these, only 51 fulfilled the diagnostic criteria of anaphylaxis. Specific data gathered from those records assessed the clinical characteristics of each case, precipitating factors, severity of the reaction and outcome. A standard form was used for data gathering. A grading system was utilized to classify

the severity of the clinical episodes.

**Results.** Cutaneous features were the most commonly found manifestations of anaphylactic reactions in the studied group. Only reactions graded 2 and 3 were identified. Reactions to medications were the most frequent identifiable causes of the entity. Multiple sensitivities to different allergens were not predictive of this clinical condition.

**Conclusions.** The identification in this study that only cases with the more severe grades of anaphylaxis were evaluated and treated at our center, the inability to recognize an inciting cause in about one third of the patient sample and the fact that a minority of the treated patients received subsequent follow-up by an allergist, reflect the need to promote the training of physicians in the field of allergy in Puerto Rico and the continued education of all physicians in the Island regarding this clinical disorder.

**Key words:** Anaphylaxis, generalized allergic reactions, immediate hypersensitivity, IgE-mediated reactions

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**A**naphylaxis is an immediate, life-threatening reaction resulting from the release of preformed and newly synthesized mediators from mast cells and basophils, following the combination of an antigen to fixed IgE on these cells. Initially described by Portier and Richet in 1902 (1), it is a type I hypersensitivity reaction, as defined by Gell and Coombs. Exogenous antigens such as food and drugs have been described to interact with IgE bound to mast cells and basophils with resultant release of histamine and other bioactive mediators (Figure

1). Whenever mast cell mediator release occurs by a direct, non-IgE-mediated process, the term anaphylactoid reaction should be used.

Anaphylaxis occurs in all age groups and prior exposure to an antigen is essential for its development. Although it has been very difficult to identify the true incidence of anaphylactic reactions, mostly due to under diagnosis and underreporting, the estimated fatality rate in the United States is 500-1000 cases per year (2, 3, 4). Age, gender, atopic history, route of exposure and prior history of an anaphylactic episode influence the likelihood of an individual experiencing a reaction to a particular agent.

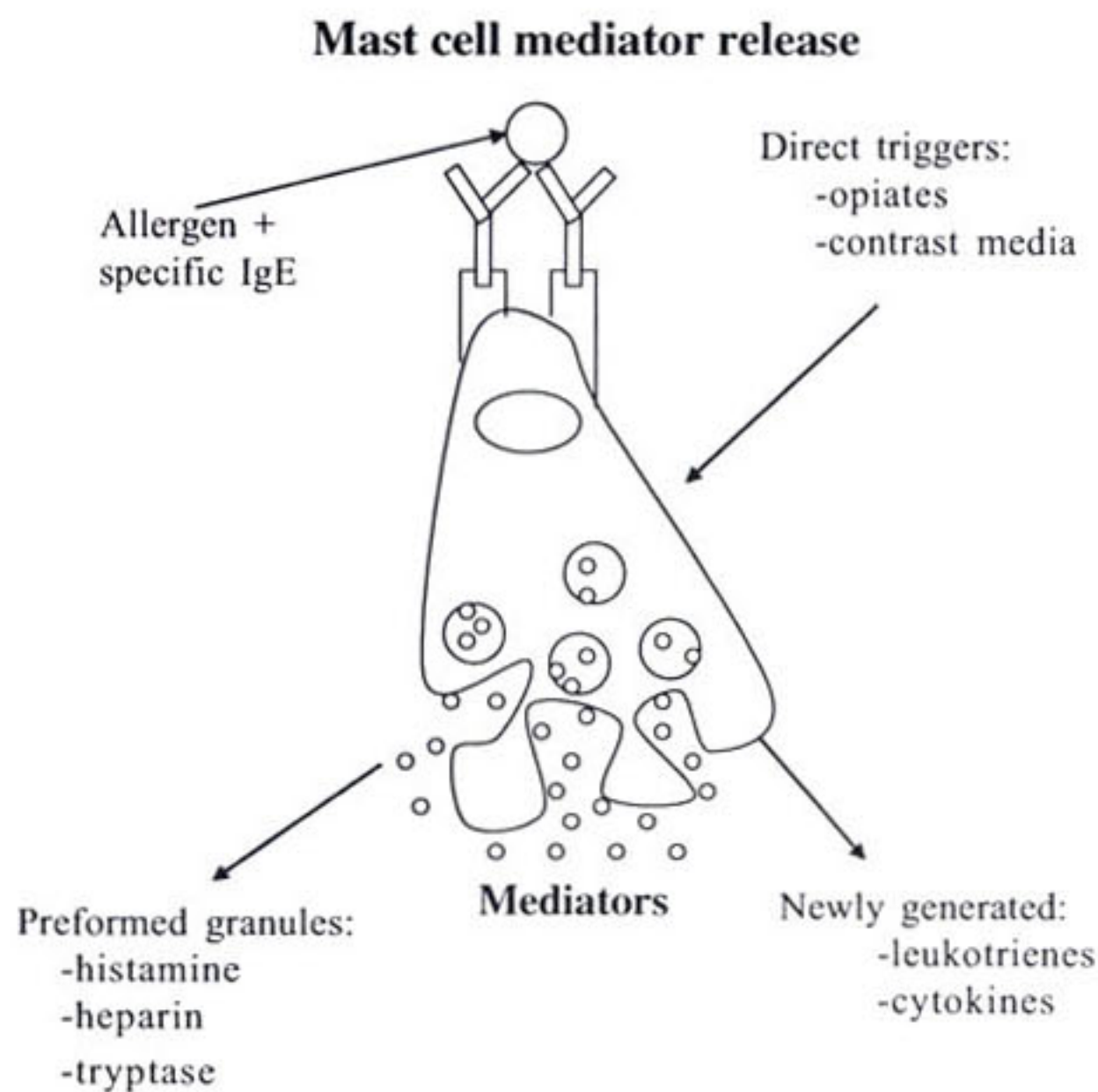
The most common causes of anaphylaxis in the United States include: insect bites, drugs, radiographic contrast media, blood products, foods, and less commonly, latex, exercise-induced and idiopathic (5). Idiopathic anaphylaxis has a 48% association with prior history of allergies (6).

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**Figure 1.** Cross-linking of IgE receptors on the surface of mast cells lead to a series of reactions terminating in mediator release. Non-allergen (or direct) triggers of mast cell mediator release include: physical factors (e.g. exercise, cold, heat, sunlight/UV radiation), medications and ethanol (anaphylactoid reactions). Preformed mediators are released within 5 minutes, whereas newly formed ones, like cytokines, may take hours.

The clinical manifestations of anaphylaxis are directly related to the mediators released from mast cells and basophils. Anaphylaxis almost always involves the skin or mucous membranes and presents with some combination of urticaria, erythema, pruritus or angioedema. Increased mucous secretion and increased muscle tone, as well as airway edema, contribute to the respiratory symptoms observed. Cardiovascular effects result from decreased vascular tone and capillary leakage. The upper respiratory tract is commonly involved, with complaints of nasal congestion, cough, hoarseness or a sensation of tightness in the throat. Dyspnea is present in patients with bronchospasm or upper airway edema. Hypoxia may cause weakness, dizziness or syncope. Chest pain may occur due to bronchospasm, secondary to hypotension and hypoxia. Gastrointestinal symptoms with cramp-like abdominal pain, nausea, vomiting or diarrhea may also occur.

The differential diagnosis of anaphylaxis includes: vasovagal reactions, other forms of shock (hypovolemic, cardiogenic, endotoxic), flushing syndromes, ingestant-related reactions (sulfites, monosodium glutamate), C1 esterase deficiency syndromes, among others.

In view of the myriad of clinical presentations, a grading system has been utilized to guide treatment efforts (Table

1). Ethnic differences in the incidence or severity of anaphylaxis have not been described, but socioeconomic differences may influence the possibility of exposure to noxious agents.

**Table 1.** Grading system for generalized hypersensitivity reactions (Adapted from reference 8)

Grade	Defined by
1. Mild	Skin and subcutaneous tissues only: generalized erythema, urticaria, periorbital edema or angioedema
2. Moderate	Features of respiratory, cardiovascular or gastrointestinal involvement: dyspnea, stridor, wheeze, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, or abdominal pain
3. Severe	Hypoxia, hypotension or neurologic compromise: cyanosis or SaO <sub>2</sub> ≤92% at any stage, hypotension (SBP < 90 mm Hg) confusion, collapse LOC or incontinence

SBP = systolic blood pressure; LOC = loss of consciousness

The aim of this study is to describe the clinical characteristics, precipitating factors, severity of the reaction and outcome of patients with this disorder seen at the Puerto Rico Medical Center over a ten-year period.

## Methods

**Study patients.** The study group comprised patients seen at the emergency room, ambulatory clinics and in the University Hospital on occasion of an episode of anaphylaxis. A retrospective and concurrent analysis of the records of such patients was conducted over a ten year period. For inclusion in the study, the patient had to be an adult (over 18 years of age) and fulfill the diagnostic criteria of anaphylaxis (7). Initially, 83 records were identified, and after applying the aforementioned criteria, only 51 patients were entered into the study.

The clinical data of all the patients included in the study was entered on a standard data sheet, which included specific questions about the previous medical history as well as the patient's access to medical care facilities. For uniformity, the clinical manifestations were classified by system involvement in terms of: general, skin, gastrointestinal, respiratory, cardiovascular and neurological (8). The magnitude of the clinical presentation was assessed as mild (skin and subcutaneous tissues only), moderate (respiratory, cardiovascular or gastrointestinal involvement) and severe (hypoxia, hypotension or neurologic compromise). Blood gases documented hypoxia and hypotension was defined when the systolic blood pressure was less than 90 mm Hg.



**Laboratory parameters.** In those records where it was available, complete blood count with specific interest in eosinophilia was looked into. In addition, the level of IgE was reviewed, when recorded in the chart.

Statistical analysis. Percentile distributions were calculated to describe demographic and clinical features of the study group. Fisher's exact test was used to determine which clinical parameters were significantly associated to hypotension and cyanosis. A p value less than or equal to 0.05 was considered to represent a statistical significant difference.

## Results

Of the original 83 records identified by the diagnostic code of anaphylaxis over a ten-year period, only 51 fulfilled the inclusion criteria. Among the excluded entities were: minor allergic reactions, hereditary angioedema, vasovagal reactions and hypovolemic shock. Incomplete records were also discarded. The population studied comprised 27 males and 24 females with age ranges as shown in Table 2.

**Table 2.** Age distribution of patients with anaphylaxis (n=51)

Age range	(n)	%
18-34	26	51.0
35-60	19	37.3
≥ 60	6	11.8

Using the grading system presented by Brown (8), the group of patients pertained predominantly to the grade-2 category (Table 3). There was not sufficient data in the records to relate the severity of the reaction with comorbidities, like pre-existent heart or pulmonary disorders.

**Table 3.** Patient population defined in terms of grade of anaphylaxis (n=51)

Grade	(n)	%
1	0	0.0
2	32	62.7
3	19	37.3

A breakdown of identified precipitating causes is presented in Table 4. There was almost the same number of patients with reactions to medications as idiopathic reactions.

As shown in Table 5, multiple sensitivities occurred in the majority of patients with a previous history of atopy.

Table 6 describes the individual clinical features associated with documented hypotension or hypoxia. The

**Table 4.** Causes of anaphylaxis related to the current episode (n=51)

Causes	(n)	%
Medications	20	39.2
Penicillin	7	13.7
Aspirin	4	7.8
NSAID	4	7.8
Sulfa	1	2.0
Other antibiotics	4	7.8
Food	9	17.6
Exercise	1	2.0
Latex	1	2.0
Anesthesia	1	2.0
Idiopathic	19	37.3

**Table 5.** Previous atopic conditions in anaphylaxis population (n=36)\*

Condition	(n)	%
Multiple sensitivities	13	36.1
Foods	8	22.2
Bronchial asthma	6	16.7
Allergic rhinitis + asthma	6	16.7
Allergic rhinitis	2	5.6
Radiocontrast media reaction	1	2.8

\* Fifteen patients had no previous history of allergic conditions

features showing the highest correlation with hypotension in the 14 patients who presented that finding were related to the gastrointestinal (nausea, vomiting and abdominal pain) and some respiratory (cyanosis and wheezing) manifestations. In terms of hypoxia, six patients had this parameter documented in the record and it was more commonly associated to some respiratory (wheezing) and neurological (dizziness, pre-syncope) symptoms. Cutaneous features were by far the most common feature in the studied sample.

Of patients that had received some type of therapy prior to arrival to the Puerto Rico Medical Center (45), all of them had received an H<sub>1</sub> antagonist, forty two had received an H<sub>2</sub> antagonist, nineteen had been administered epinephrine and seven had been treated with steroids.

Forty-three patients had IgE levels sampled, of which only seventeen were elevated. Of the forty-nine patients with eosinophil counts in the records, eosinophilia was present in 29 cases.

Of the thirteen patients with prior history of systemic reactions only two were carrying some sort of identification as being an allergic person and only six had been properly instructed on self-administration of epinephrine. Six patients out of the total population studied had been exposed to immunotherapy in the past.



**Table 6.** Individual clinical features associated with documented hypotension or hypoxia (n=51)

Clinical feature	Number and percent with hypotension and /or hypoxia		Hypotension		Cyanosis	
	(n)	%		p value		p value
<b>Cutaneous</b>						
Urticaria/angioedema	41	80	1	<0.001	0	<0.001
Flushing	30	59	0	<0.001	0	<0.001
Pruritus	6	11	0	0.170	0	0.170
<b>Respiratory</b>						
Wheezes	11	21	7	0.005	6	0.050
Upper airways edema	18	35	6	0.525	6	0.525
Chest pain	9	17	3	0.692	3	0.692
Dyspnea	33	64	8	0.525	6	0.566
Rhinitis	7	13	0	0.169	0	0.169
Cyanosis	6	11	5	0.004	6	-
<b>Cardiovascular/Neurologic</b>						
Dizziness (pre syncope)	13	25	5	0.309	0	0.010
Diaphoresis	14	27	4	1.00	1	0.077
Confusion	6	11	2	0.661	6	0.000
Loss of consciousness	10	19	8	0.000	4	0.432
Hypotension	14	27	14	-	5	0.489
Headache	21	41	1	0.003	0	0.000
<b>Gastrointestinal</b>						
Nausea	35	68	9	0.741	1	<0.001
Vomiting	23	45	10	0.029	2	0.010
Diarrhea	29	56	13	0.001	1	0.000
Abdominal pain	15	29	5	0.731	1	0.041
Incontinence	3	5	3	0.017	0	0.552
<b>Systemic</b>						
Weakness	18	35	0	0.000	0	0.000
Malaise	18	35	0	0.000	0	0.000
Anxiety	29	56	0	<0.001	0	<0.001

Regarding outcome of the study group three patients died; sixteen continued under follow-up with an allergist and thirty-two by their primary physicians. The three deaths were seen in patients over 60 years of age and had concomitant diabetes, hypertension and coronary artery disease.

## Discussion.

This study is in agreement with previously published series, which have documented that the majority of the patients presenting with a clinical picture of anaphylaxis belong to younger adult-range age groups (9). Moreover, all the patients in this study with grade 3 reactions were over 50 years of age. The relation of age as a major determinant of the severity of the reaction has also been reported in other studies (10). Since no patients in the pediatric age were included, a complete analysis of the

frequency of anaphylaxis in all age groups cannot be made.

In the study group there was similar representation of episodes related to medications as well as those with unknown causality. This observation may be unrealistic, since idiopathic anaphylaxis requires continued evaluation and reassessment over time to exclude an identifiable but elusive cause. Some investigators consider idiopathic anaphylaxis a controversial entity and insist that with appropriate follow-up and diagnostic procedures, a cause can be established in most cases (11). The finding of medications as the most frequent etiology of anaphylaxis in the study group is not consistent with most reports in which insect stings have been the most frequently identified inciting agent.

Our findings indicate that having an atopic history is not predictive of anaphylaxis, as shown by an almost equal proportion of patients without it. However, this data could be skewed, as the physicians that interviewed the patients were not allergists.

Skin involvement (urticaria/angioedema) was very common in our series even when the grades of anaphylaxis were in the 2 to 3 range, however these manifestations were not generalized. Patients presenting with laryngeal angioedema, which is considered the most serious manifestation of angioedema, had concomitant involvement of another organ, thus allowing their inclusion in groups of a higher grade of anaphylaxis. For these previous reasons, there were no cases that could be classified in the grade 1 category. The results presented here support a definition of anaphylaxis that includes only features listed in the moderate and severe categories or that necessitates generalized skin/mucosal features with additional organ involvement. The absence of generalized skin involvement in the studied population could be related to the fact that at the time of arrival to our facility the patients had received various forms of treatment (especially H<sub>1</sub> antagonists) and to the identification of skin manifestations as allergic reactions (not as anaphylaxis) treatable at primary healthcare centers.

Overall, cutaneous manifestations were the most frequently represented.

A trend was observed regarding an association of hypotension with some gastrointestinal manifestations, which is in agreement with findings in other reported series (8). This correlation may be explained in terms of direct mediator effects or poor perfusion at tissue level prior to the onset of hypotension. In the limited number of patients with hypoxia, there was a tendency for association with some respiratory and neurological features, consistent with involvement of vital organs and the prediction of more severe complications.

The use of epinephrine, considered the mainstay of



treatment for anaphylaxis, was scanty in this series. Possible explanations for this might be that the patients were in a different condition when first seen at local health centers or that some manifestations were missed by physicians who saw the patients initially.

The fact that only sixteen patients of the total population had subsequent follow-up by an allergist, reflects the limited resources of trained physicians in this field in Puerto Rico. After an anaphylactic reaction, it is appropriate that a fully trained allergist evaluate each patient thoroughly.

### Limitations

Reliance on medical records for the information is a limitation of the study since the accuracy of the recorded documentation is variable among physicians. In addition, the size of the sample analyzed sets limits to the observed results. A continued surveillance of patients with anaphylaxis should be planned so that a larger patient sample could be examined and particularly assess the cases reported as idiopathic anaphylaxis over time.

Since anaphylaxis occurring in the community often recovers spontaneously, it is important to educate the public in general about this condition in order to: 1) diagnose the condition as soon as possible, 2) avoid identified risk factors, and 3) encourage physicians to refer all individuals with a prior episode of anaphylaxis to an allergist-immunologist (12).

### Resumen

Este estudio analizó las características clínicas, los factores precipitantes, la severidad de las reacciones y la evolución clínica de un grupo de pacientes referidos para evaluación al Centro Médico de Puerto Rico con el diagnóstico de anafilaxis en un período de 10 años. El análisis permitió además, comparar los datos recopilados con series similares informadas en la literatura médica. El análisis consistió de un cernimiento inicial, de forma retrospectiva y concurrente, de 83 expedientes médicos de pacientes con el diagnóstico de anafilaxis, de los cuales 51 cumplieron con los criterios clínicos para el diagnóstico de esa condición. La recopilación de datos se efectuó mediante la utilización de un formulario en el cual las reacciones informadas en los expedientes fueron clasificadas en términos de su severidad en una gradación

del uno al tres. Las lesiones cutáneas (urticaria y angioedema) fueron las lesiones más frecuentemente observadas como manifestaciones de anafilaxis. Las reacciones a medicamentos fueron la causa predominante identificada. No se encontró evidencia de que un antecedente de sensibilidad a múltiples alérgenos estuviera relacionado a una más alta posibilidad de desarrollar la condición. Todos los pacientes evaluados pertenecieron a las gradaciones de severidad 2 y 3. No fue posible identificar un factor precipitante en una tercera parte de los casos. Sólo una minoría de los casos referidos fueron subsiguientemente evaluados y seguidos por un especialista en alergia. Se concluye que estas tres últimas aseveraciones ponen de manifiesto la necesidad de que se promueva el adiestramiento de especialistas en esta disciplina en Puerto Rico y a la misma vez se fomente la educación continua de todos nuestros médicos sobre esta importante entidad clínica.

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