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## Characteristics, Etiology and Treatment of Pediatric and Adult Anaphylaxis in Iran

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### ABSTRACT

Despite the increasing prevalence of anaphylaxis, there is little information about the characteristics and practice of healthcare providers in treating anaphylaxis, so this study was conducted to record the characteristics and therapeutic approaches of anaphylaxis from May 2012 until April 2015, the data of all patients diagnosed with anaphylaxis in the Allergy department of three referral university hospitals in Tehran, Iran were recorded. Thereafter, the demographics, clinical features, triggers and therapeutic approach were evaluated.

This study investigated 136 individuals, 64 males (47%) between 6 months and 68 years old, as well as 72 others (52.94%) under 18 years of age (pediatric). The following were the most common organs involved: Skin 86.02% (pediatric 91.66% vs adult 79.68%), respiratory tract 51.47% (pediatric 43.05% vs adult 60.93%), cardiovascular 50.73% (pediatric 54.16% vs adult 46.87%), gastrointestinal 20.58% (pediatric 27.7% vs adult 12.5%) and neurologic system 5.88% (only in adults). The following were the most identified causing foods 69 (50.37%) [42 pediatric (children) and 27 adults], drugs 34(25%)[14 pediatric and 20 adults], idiopathic 16(11.77%) [3 pediatric and 13 adults], insect sting 7(5.15%) [3 pediatric and 4 adults], exercise 6(4.42%) [1 pediatric and 5 adults]. Milk, egg and wheat were the most common causative foods in pediatric cases but sesame, as well as egg and milk were the most common causes in adults. Epinephrine injection, auto injector epinephrine prescription as a discharging plan and referral to an allergist were: 10.78, 1.96 and 7.8 %, respectively.

In this case series we found that, cutaneous, respiratory, cardiovascular and gastrointestinal complains were the most common manifestations and food, drug and idiopathic were the most common causes.

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In this study, the diagnosis of anaphylaxis, epinephrine subscription and referral to an allergist were significantly lower in comparison to other studies.

**Keyword:** Adult anaphylaxis; Anaphylaxis registry; Anaphylaxis etiology; Anaphylaxis treatment; Children anaphylaxis

## INTRODUCTION

Anaphylaxis is defined as a systemic, rapid onset and potentially life-threatening hypersensitivity reaction. It is a clinical emergency so all healthcare providers should be familiar with its management.<sup>1-4</sup> The diagnosis of anaphylaxis is based on history and physical exam and it is very critical considering that there is a broad spectrum of presentations and shock is just an uncommon manifestation in anaphylaxis and relying on it can result in the under diagnosis of anaphylaxis.<sup>5,6</sup> Defining the exact prevalence of anaphylaxis is difficult and it seems that there is under diagnosis and consequently, under correct treatment of this condition. However, on the other hand, based on literature, the prevalence and incidence of anaphylaxis is increasing all over the world.<sup>7-9</sup> There are different reasons for the potential fatality of anaphylaxis including similarity with other diseases, under estimating the condition in parallel with the delay and under usage of epinephrine.<sup>10-12</sup> Different barriers have been determined in literature as the main reasons for malpractice in anaphylaxis. Correct and rapid diagnosis, epinephrine injection in the first line and having a correct discharging plan are the main steps in managing anaphylaxis.<sup>6,10,13</sup> In the first step, this retrospective study was conducted in all individuals diagnosed with anaphylaxis by an allergist in the allergy department of three referral university hospitals between 2012-2015. In this study, the following were recorded clinical manifestations, causative trigger and treatment approach during attacks and discharging plans in the acute phase and the recurrence of attacks before and after visiting an allergist and determining the causative etiology. This study was approved by the ethical board in Iran University of Medical Sciences.

## MATERIALS AND METHODS

This retrospective study was performed and included all patients who came to the outpatient clinic of the Allergy department in 3 referral university hospitals: Rasool e Akram, Ali Asghar and Firoozabadi, affiliated

to Iran University of Medical Sciences from May 2012 until April 2015. Individuals diagnosed with anaphylaxis were selected based on anaphylaxis criteria by an allergist and accepted to be investigated. The study was approved by Research Ethics Committee of Iran university of Medical sciences with approval number: 96/105/546 and all participants provided written informed consent. Data were collected using a standard questionnaire which focused on these items: (1) demographic data; (2) atopic status of the patient and the family; (3) the symptoms of anaphylactic event, (4) the course of anaphylaxis including the time lapse between contact with the trigger and onset of symptoms, the first symptom of the reaction, total duration of symptoms, and being biphasic or not; (5) the treatment: drugs and admission; (6) discharging plan including: action plan, referral to an allergist, epinephrine prescription, (7) recurrence before and after visiting the allergist, and (8) the causative trigger of anaphylaxis.

### Determining the Etiology

The discovery that food, insect bites or drugs are the causative trigger for anaphylaxis was based on a clear and relative history of anaphylaxis onset within hours after exposure to the causative agent, skin prick testing and/or in some cases by serum specific IgE (sIgE) testing (Phadia250 Detection System, ImmunoCAP, Phadia AB, Sweden). Serum sIgE levels  $>0.35$  kU/L were considered positive and skin prick testing was performed based on approved methods in the allergy clinic.<sup>14</sup> Idiopathic anaphylaxis was diagnosed if the medical history did not suggest a clear trigger and all allergen tests were negative. As a result of the potential risks of triggering anaphylaxis with oral challenges, oral food or drug challenges were not performed.

### Statistical Analysis

All analyses were performed using SPSS software version 10.0 (SPSS Inc., Chicago, IL, USA).

A descriptive analysis was used for the demographics of the study group. Non-parametric variables were analyzed with the Pearson chi-square

test or the Fisher's exact test when needed. The Wilcoxon-Mann-Whitney U test and Kruskal-Wallis one-way ANOVA were used to compare age, time lapse between contact with the trigger and onset of symptoms, time lapse between the onset of symptoms and administration of medications, and the total duration of symptoms between two or more groups.

## RESULTS

### Demographic Characteristics

This case series consisted of 136 individuals who were aged between 6 months and 68 years ( $21.01 \pm 15.26$  years), 64 males (47%) with no difference between sexes ( $p > 0.05$ ). The demographic data and allergy history are explained below (Table 1).

### Timing

In 46 (33.82%) cases, anaphylaxis happened less than 5 min (very rapid attack) after exposure to the causative agent and it was significantly more prevalent in children ( $p < 0.05$ ). Attacks happened between 5-60 min (rapid attack), after exposure in 38 individuals (27.94%) without difference in children and adults ( $p > 0.05$ ) and in 32 (23.52%) of them attacks happened after 1 hour (delayed attack) with more significant prevalence in adults ( $p < 0.05$ ), 20 patients were not oriented to the onset of attack and biphasic reactions were presented in 6 patients (4.41%).

### Organ Involvement

The following were the most prevalent organs involved: Skin (86.02%), respiratory organ (51.47%), cardiovascular (50.73%), gastrointestinal tract (20.58%) and neurologic system (5.88%). GI involvement was significantly ( $p < 0.05$ ) more prevalent in pediatrics while neurologic manifestation was only seen in adults, vaginal bleeding occurred in 3 adult females. The manifestations are shown in Table 2.

### Etiology

In 87 of the 136 participants (63.97%), the patients' suggestions about the cause of their anaphylaxis were correct but 49 of them (36.02%) could not determine if their suggestion was wrong. Food (50.73%), drug (25%), idiopathic (11.76%), insect sting (5.14%) and exercise (4.41%) were the most common culprits in our case series. Milk (n=17), egg (n=9) and wheat (n=9) were the most causative foods in pediatric but egg

**Table 1. Demographics and allergy history in anaphylactic patients**

Characteristics	N (%)
Adult (>18y)	64(47.05%)
Pediatric (<18y)	72(52.95%)
Male	64(47%)
Female	72 (53%)
Personal allergy history	
Food allergy	40 (29.4%)
Allergic rhinitis	39(28.67%)
Asthma	36(26.47%)
Atopic dermatitis	34(25%)
Urticarial & angioedema	23(16.91%)
Drug allergy	13(9.55%)
Clinical presentations	

(n=6), sesame (n=6) and milk (n=5) were more (n=6), sesame (n=6) and milk (n=5) were more prevalent in adults. NSAIDs, antibiotics and anticonvulsants were the most causative drugs but NSAIDs were more prevalent in adult cases while antibiotics were more prevalent in pediatrics. Three of our patients experienced food dependent and exercise induced anaphylaxis, one pediatric with wheat and two adults with shrimp and pistachio (Table 3).

### Recurrence Rate

A total of 51 (37.5%) individuals experienced one anaphylactic attack but 85(62.5%) experienced more than one attack. In total, 226 cases of anaphylaxis were documented in these 85 individuals. In 8 individuals, the second attack occurred less than one month, 33 individuals between 1 month and one year and 44 individuals could not remember the exact time of the second attack.

The most common causes of repeated anaphylaxis were food (n=50), idiopathic (n=13), drug (n=11), exercise (n=6) and venom sting (n=5). It was only in one case that the second anaphylaxis trigger differed from the first episode. The rate of anaphylaxis recurrence was significantly higher ( $p < 0.05$ ) before visiting an allergist and determining the causative etiology, as 64 of 85 individuals experienced 165 anaphylaxis before visiting and 21 of them had 61 attacks after determining the cause by an allergist. In the group which was alert to their diagnosis and its trigger; food (n=9), idiopathic (n=8), drug (n=2) and venom sting (n=2) were the most causes and they were unavoidable, hence their orientation.

**Treatment**

A total of 102 of 136 individuals visited emergency departments during the symptomatic phase but 34 of them did not go during attacks, from 102 patients 25 individuals were admitted (24.5%) more than 4 hours, 33 individuals were admitted less than 4 hours (32.35%) and 44 individuals were quickly discharged soon after

visit (43.13%). H1 anti-histamines followed by systemic corticosteroids were the most common prescription in symptomatic individuals; epinephrine was prescribed in 11 individuals (10.78%). As a discharging plan, auto injection of epinephrine was prescribed in 2 individuals (1.96%) and 8 of them were referred to an allergist (7.8%). Treatment is shown in Table 4.

**Table 2. Organ involvement in anaphylactic patients**

Organ involvement	Pediatric: n (%)	Adult: n (%)	Total: n (%)
Patients	72 (52.94%)	64 (47.05%)	136 (100%)
Skin	66 (91%)	51 (79.98%)	117 (86.02%)
Respiratory	31 (43.05%)	39 (60.93%)	70 (51.47%)
Gastrointestinal	20 (27.77%)	8 (12.5%)	28 (20.58%)
Cardio vascular	39 (54.16%)	30 (46.87%)	69 (50.73%)
Neurologic system	0 (0%)	8 (12.5%)	8 (5.88%)
Others:			
Vaginal bleeding	0 (0%) 3	(4.68%)	3 (2.2%)

**Table 3. Causative factors in pediatric and adult anaphylaxis**

Cause	Pediatric: n (%)	Adult: n (%)	Total: n (%)
Patient	72	(52.94%) 64	(47.05%) 136
Food	42 (58.33%)	27 (42.18%)	69 (50.73%)
Milk	17 (23.61%)	5 (7.81%)	22 (16.17%)
Egg	9 (12.5%)	6 (9.37%)	15 (11.02%)
Wheat	9 (12.5%)	2 (3.12%)	11 (8.08%)
Sesame	1 (1.38%)	6 (9.37%)	7 (5.14%)
Hazelnut	2 (2.77%)	3 (4.68%)	5 (3.67%)
Almond	1 (1.38%)	0 (0%)	1 (0.73%)
Peanut	2 (2.77%)	1 (1.56%)	3 (2.2%)
Peach	0 (0%)	2 (3.12%)	2 (1.47%)
Saffron	0 (0%)	2 (3.12%)	2 (1.47%)
Kiwi	1 (1.38%)	0 (0%)	1 (0.73%)
Drug	14 (19.44%)	20 (31.25%)	34 (25%)
Penicillin	3 (4.16%)	5 (7.81%)	8 (5.88%)
Ceftriaxone	0 (%)	2 (3.12%)	2 (1.47%)
Co-trimoxazol	2 (2.77%)	1 (1.56%)	3 (2.2%)
NSAIDs	0 (0%)	14 (21.87%)	14 (10.4%)
Phenobarbital	3 (4.16%)	1 (1.56%)	4 (2.94%)
Lamotrigine	2 (2.77%)	0 (0%)	2 (1.47%)
Losartan	0(0%)	1 (1.56%)	1 (0.73%)
Idiopathic	3 (4.16%)	13 (20.31%)	16 (11.76%)
*Exercise	1 (1.38%)	5 (7.81%)	6 (4.41%)
Venom sting	3 (4.16%)	4 (6.25%)	7 (5.14%)
**Vaccine	3 (4.16%)	0 (0%)	3 (2.2%)
Latex	0 (0%)	1 (1.56%)	1 (0.73%)

\*3 of them were food dependent exercise induced anaphylaxis (one pediatric and two adult)

\*\*all of them were due to MMR vaccine (mumps, measles and rubella)

**Table 4. Treatment and discharging plan in anaphylactic patients**

Information about treatment and discharging plan	Number (percent)
No emergency department (ED) visit during symptomatic phase	34 (25%)
ED Visit during symptomatic phase	102 (75%)
Early discharge just after visit	44/102 (43.13%)
Admitted but discharged before 4 hours	33/102 (32.35%)
Admitted and discharged after 4 hours	25/102 (24.5%)
Drugs prescribed in ED	
Systemic H1 anti histamine	98 (96.07%)
Systemic corticosteroids	79 (77.45%)
Epinephrine	11 (10.78%)
Discharged with correct diagnosis of anaphylaxis	6/102 (5.88%)
Referring to allergist after discharging	8/102 (7.84%)
Epinephrine auto injector prescription in discharging time	2/102 (1.96%)

## DISCUSSION

This retrospective study registered the characteristics, causative etiology and therapeutic approach with special attention to discharging plan in pediatric and adult anaphylaxis, visited and diagnosed in allergy clinics of three tertiary university hospitals in Tehran, the capital city of Iran. To our knowledge, this is the largest investigation concerning the etiology in adult population and the first study that recorded the treatment and discharging plan for anaphylaxis in Iran. Hsin YC showed that anaphylaxis is more common in adults than children (pediatric) and more common in males than females in Taiwan, and atopic dermatitis was the most prevalent allergy history especially in pediatrics.<sup>15</sup> Blackhall study in Tasmania, Australia, showed that anaphylaxis is more prevalent in adults (78.91%) vs children (21.1%) and in the adult age was more prevalent in females but in pediatric cases, it was more prevalent in males.<sup>16</sup> Our investigation showed that anaphylaxis was more prevalent in children (52.94%) than adults (47.06%) and females (53%) than males (47%); however, the *p* value was not significant (*p*>0.05). Personal and familial history of allergy was positive in 75.73 and 69.85% of individuals. A personal history of food allergy (29.4%) was the most common while drug allergy (9.55%) was the least common finding in the allergy history. It appears that the prevalence of anaphylaxis and distribution according to sex and age is dependent on the study area, duration and inclusion criteria. Since our study was limited to 3

referral hospitals, with one of them being a pediatric hospital, so maybe this is the reason for more prevalence in pediatrics. Based on previous studies, the causes of anaphylaxis vary based on the geographical location and subject selection. In the first children anaphylaxis registry in Iran, food was reported as the most common cause (89.7%) of anaphylaxis in the children population; of which milk (49.3%) and wheat (26.1%) were the most common foods followed by insect sting (4.3%),<sup>17</sup> this study was limited to pediatric field and only focused to the etiology and manifestation while our study enrolled children and adult data and focused on management in addition to manifestation. A study of patients from an outpatient allergy clinic in Central Europe showed that insect bites were the most common cause of anaphylaxis,<sup>18</sup> while in South Korea, emergency patients reported drugs as the most common cause.<sup>19</sup> A study based on two nationwide surveys showed that the most common triggers of anaphylaxis in the American population were medications (34%), foods (31%), and insect stings (20%).<sup>20</sup> However, Jiang et al showed that foods are the most common cause (77%), followed by idiopathic factors (15%), medications (7%) and insects (0.6%) in a tertiary center in China and milk is the most common trigger in pediatrics followed by fruits and vegetables and wheat as the most common trigger in adults. In a previous study, 7% of anaphylactic reactions was triggered by drugs in which herbs were the most common followed by antibiotics.<sup>21</sup> In our study, the most common causative triggers in children and adults were foods



(pediatric 58.33% vs adult 42.18%,  $p>0.05$ ), drug (pediatrics 19.44% vs 31.25,  $p<0.05$ ), idiopathic (pediatric 4.16% vs adult 20.31%,  $p<0.05$ ) and sting (pediatric 4.16% vs adult 6.25%,  $p>0.05$ ). In comparison to studies from other countries, unique patterns of food-induced anaphylaxis were observed for Iranian adult patients. In adults, sesame (22.22%), egg (22.22%), milk (18.51%), hazelnut (11.11%) and saffron (7.4%) were the most common triggers, respectively. To our knowledge, such a high proportion of some foods has not yet been reported in Western countries, which may be related to the different life styles and different food consumption. For example, sesame is used in large amounts in different foods in Iran and saffron is one of the most common additives used in Iran. In contrast to North American countries where peanut was an important trigger,<sup>22,23</sup> in our study hazelnut was more common than peanut, however neither hazelnut nor peanut were common triggers. The recurrence of anaphylaxis is not an unusual problem and this makes it more complex. It is estimated that one-third of cases present with recurrent anaphylaxis.<sup>24</sup> It appears that there are many reasons for the recurrence of anaphylaxis including: incorrect or delayed diagnosis of anaphylaxis, incorrect determination of the causative etiology, cross reactivity between causes and incidental exposures to the cause.<sup>25,26</sup> There is insufficient data about recurrent anaphylaxis, especially when mast cell disorders are excluded.<sup>27-29</sup> Based on the literature, all patients with anaphylaxis do not have the same risk of recurrence. Patients with drug anaphylaxis have a lower risk<sup>30</sup> but in exercise-induced, idiopathic and food anaphylaxis the chance is increased.<sup>25,30-32</sup> It seems that the etiology of recurrent anaphylaxis is dependent on the geographic area and the age of patients included for investigation. For example, in some areas, venom stings are the main cause of recurrence<sup>33,34</sup> but O'Keefe et al showed that food is the main culprit responsible for recurrent anaphylaxis in children in Canada.<sup>25</sup> To the best of our knowledge, this study is the only investigation that has focused on this problem in Iran. Records were taken before and after visiting the allergist. Our study showed that confirming the diagnosis and determining the etiology, significantly ( $p<0.05$ ) decreased the rate of anaphylaxis attacks in cases with recurrent anaphylaxis. However, in 61 of 85 cases with repeated anaphylaxis, the attack happened despite documenting the diagnosis and finding out the

trigger. So, according to our study, the rate of anaphylaxis will decrease after referral to the allergist but it is not totally avoidable especially in the case of food, idiopathic causes, exercise and venom sting anaphylaxis. In all ages, epinephrine is the most important drug recommended in anaphylaxis and it is strongly advised to inject it rapidly after diagnosis.<sup>2,5,35-37</sup> Despite practical guidelines in the field of anaphylaxis, it seems that the approach of healthcare providers to anaphylaxis management is not optimum in different countries. In a global survey of 52 countries, World Allergy Organization showed that anaphylaxis guideline and essential drugs, especially epinephrine in emergency settings, are available only in 31 of the 52 countries which participated in this investigation.<sup>38</sup> Mostmans et al showed that the ED physicians in the St. Pierre hospital in Brussels used epinephrine in 67% of anaphylaxis and referred 74% of their cases to the allergist after discharging from the ED.<sup>39</sup> Epinephrine injection in ED, auto-injection epinephrine prescription as a discharging plan and referral to the allergist for further evaluation were 47, 61 and 45%, respectively, in Arkansas children hospital.<sup>40</sup> It was found that the Epinephrine injection rate in anaphylaxis is not optimum in all countries. Abdullah et al showed that epinephrine prescription and referral to the allergist were 3.2 and 16% in Riyadh, Saudi Arabia.<sup>41</sup> Also, there was 15.9% epinephrine injection in anaphylaxis attack and 4.5% auto-injection of epinephrine prescription as discharging plan in Lebanon.<sup>42</sup> In our study, 102 of 136 individuals with anaphylaxis went to ED during their acute phase. In these cases, epinephrine injection in ED, auto-injection of epinephrine prescription and referral to the allergist were: 10.78, 1.96 and 7.8%, respectively. It seems that there is a significant under prescription of epinephrine in the management of anaphylaxis in our hospitals.

This study showed that: skin, cardiovascular and respiratory systems were the most commonly involved organs in pediatric anaphylaxis as: 91.66, 54.16 and 43.05%, respectively but skin, respiratory and cardiovascular were: 79.68, 60.93 and 46.87 % in adults.

Foods, drugs, idiopathic causes and venom sting were the most common triggers. Milk, egg and wheat were the most causative foods in pediatrics but sesame, egg, milk and saffron were the most causative foods in adults. It was found that 62.5% of cases had more than

one attack. Food, idiopathic causes, drug and exercise were the most causative triggers in repeated anaphylaxis. Visiting an allergist and determining the cause could significantly decrease the rate of recurrent anaphylaxis; however, in the case of food, idiopathic and drug, repeated anaphylaxis occurred, despite documentation of the correct diagnosis and determining the etiology. Based on the guidelines epinephrine is the only permanent drug in anaphylaxis and a patient may meet anaphylaxis once in a life and could result in death or survive with a simple injection so it is critical to aware the role and importance of it in anaphylaxis. Epinephrine injection, auto-injection of epinephrine prescription and referral to an allergist were significantly low in our study, however this study was done in 3 centers and could not present the whole picture of anaphylaxis characteristics and management in Iran and larger studies are necessary in this field.

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