

# Is adrenaline misused in anaphylaxis treatment? Experience of a large, urban Emergency Department: review of 589 cases.

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## Abstract

**Objective.** Acute allergic reactions are important causes of Emergency Department (ED) admissions. Although the current recommendations for treatment of patients with anaphylaxis are focused on the central role of adrenaline, evidence in support of this therapy is still scarce. We planned a retrospective analysis of all allergic and anaphylactic reactions managed in the ED, to assess adherence to current guidelines and clinical outcomes.

**Methods.** The study population consisted of all consecutive adult patients admitted to the ED with acute allergic reactions during the year 2013. Overall, the final study population consisted of 589 patients, i.e., 329

women and 260 men (55.9% vs. 44.1%, mean age 43±18 years, range 16-96 years).

**Results.** Fifty-six patients were diagnosed with anaphylaxis (9.5%), 75 with angioedema (12.7%), 363 with urticaria (61.7%), and 95 with urticaria-angioedema (16.1%). The triggers included drugs (21.9%), foods (15.0%), hymenoptera stings (9.9%), and chemicals (4.4%), whereas a specific cause could not be recognized in nearly half of the cases. Only 5 (8.9%) of 56 patients diagnosed with anaphylaxis received adrenaline and no death or Intensive Care Unit (ICU) admission occurred within one month from the acute allergic episode.

**Conclusion.** The results of our study suggest that anaphylaxis is widely undertreated with adrenaline in our local ED compared to guidelines and recommendations. Nevertheless, a favorable outcome was recorded for all patients included in the study, even when managed with second- and third-line treatments, as attested by the lack of deaths at 1 month and the very limited number of hospitalizations (3/589; 0.5%), related to comorbidities rather than to treatment failure. The strength of recommendations contained in current guidelines should hence be reconsidered.

**Key words:** allergy, anaphylaxis, urticaria, angioedema, adrenaline, epinephrine

## Introduction

Acute allergic reactions are important causes of Emergency Department (ED) admissions, the frequency of which has exhibited an incremental trend in the past decades. (1,2) Alongside allergic rhinitis, which is an infrequent cause of ED visits, and asthma (i.e., a separate disease), the most frequent types of acute allergic reactions include acute urticaria, acute angioedema and anaphylaxis, as well as an overlap of these acute conditions. Although acute urticaria is considered a self-limiting disease in the vast majority of cases, it might occasionally be associated with angioedema, or else be an important symptom of anaphylactic episodes.

(3)

Angioedema refers to a local, reversible swelling of deep skin layers of upper respiratory or gastrointestinal mucosa. Isolated angioedema may seldom present with an onset of pain and tenderness, while itching is infrequent. (4) Although angioedema does not have preferential localization, lips, mouth, tongue, neck, larynx, pharynx, abdominal or genital areas are the sites most frequently involved. (4) When the upper respiratory tract is involved, the condition turns into a real clinical emergency. As for urticaria, angioedema can also be part of the complex clinical picture of an anaphylactic reaction.

Anaphylaxis is now defined as a severe, quickly developing and frequently life-threatening allergic reaction. (5) Although the lifetime prevalence of this condition approximates 2%, its frequency has constantly increased in past years. (6) Importantly, uncertainty still exists about the precise definition, so that only 1% of ED admissions for acute systemic allergic reactions are correctly diagnosed as anaphylaxis, whereas most cases are classified as “acute allergic reactions” or “acute hypersensitivity reactions”. (7,8) From a clinical perspective, anaphylaxis should also be regarded as a continuous rather than a dichotomous state, and this probably entails different management strategies .

Although the current recommendations for treatment of patients with anaphylactic reactions are focused on the central role of adrenaline (also known as epinephrine), the evidence in support of this therapeutic approach is scarce due to the lack of well-designed controlled trials. (9-12) The therapeutic recommendations for use of adrenaline in anaphylaxis are largely based on clinical pharmacology studies, clinical observations, animal models, expert consensus, as well as by a reasonable amount of anecdotal evidence. Moreover, there are some substantial differences between guidelines, not only regarding adrenaline utilization, but even more substantially concerning the use of oxygen, anti-histamine and corticosteroids. (13) Therefore, we planned a retrospective analysis of all allergic and anaphylactic reactions managed in the ED of the University Hospital of Parma during a 1-year period, to

assess adherence to current guidelines and clinical outcomes.

## Materials and methods

The study population consisted of all consecutive adult patients admitted to the ED of the University Hospital of Parma (Italy) with acute allergic reactions during 2013. The facility is a 1250-bed teaching general hospital, serving a population of approximately 435,000 inhabitants. Information about ED visits for acute allergic reactions was acquired from the electronic hospital database during a 1-year period (1<sup>st</sup> January to 31<sup>st</sup> December 2013), using a double extraction key, i.e., ICD-9 codes 999, 995, 716, 708, 477, and 287 (including all the 4<sup>th</sup> and 5<sup>th</sup> digits), as well as verbal “strings”, i.e. “allergy”, “anaphylaxis”, “urticaria”, “angioedema”, “shock”. All cases had complete information about clinical signs, trigger(s) (when reported), pharmacological treatment, disposition and outcome. Patients’ outcome was monitored up to 1 month from records included in the hospital database, telephone calls, and search in the provincial database of deaths. The study was performed in accordance with the Declaration of Helsinki, under the terms of relevant local legislation.

## Results

A total number of 3237 records were analyzed by two separate physicians after first extraction, in order to exclude erroneous or dubious entries. Children aged 16 years or younger (n=273 cases) were not included since they are usually seen in the Pediatric Clinic of our hospital and not by Emergency Physicians (EPs). Cases of allergic rhinitis, asthma and chronic urticaria were also excluded (n=2376), so that the analysis was limited to adult patients admitted with acute urticaria, acute angioedema, urticaria-angioedema and anaphylaxis, defined according to the recommendations of the Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis

Network symposium, (5) and of the World Allergy Organization guidelines for the assessment and management of anaphylaxis. (12) Overall, the final study population consisted of 589 patients, i.e., 329 women and 260 men (55.9% vs. 44.1%, mean age 43±18 years, range 16-96 years), representing 0.65% of all ED admissions throughout the study period. All patients arrived to the ED prior to 12 hours from onset of symptoms and none of them were admitted more than once for acute allergic reactions during the study period. No patients had adrenaline administered) before ED arrival, i.e., self-administered or from pre-hospital providers. Fifty-six patients met the diagnostic criteria for anaphylaxis (9.5%), 75 for angioedema (12.7%), 363 for urticaria (61.7%), and 95 for urticaria-angioedema (16.1%). The suspected triggers of allergic reactions were drugs (n=129; 21.9%), food (n=88; 15.0%), hymenoptera stings (n=58; 9.9%) and chemicals (n=26; 4.4%), whereas a specific cause could not be recognized in nearly half of cases (n=288; 48.9%). In the subgroup of patients with anaphylaxis, the triggers were food in 17 cases (30.3%), drugs in 18 cases (32.1%), hymenoptera stings in 5 cases (8.9%), chemicals in 5 cases (8.9%), and unknown trigger in the remaining 11 cases (19.6%). The complete report of triggers for each group is reported in table 1.

The 56 patients diagnosed with anaphylaxis received adrenaline in 5 cases (8.9%), whereas chlorphenamine (an anti-H1 anti-histamine drug) was used in 35 cases (62.5%), ranitidine (an anti-H2 anti-histamine drug) in 32 cases (57.1%), methylprednisolone in 40 cases (71.4%) (in most cases, drugs were used in combination). In 24 cases (42.9%) other therapeutics (mainly crystalloids, oxygen, salbutamol) were administered. The patients with angioedema were treated with chlorphenamine in 53 cases (70.7%), ranitidine in 24 cases (53.3%) and methylprednisolone in 58 cases (77.3%). None of these patients received adrenaline. Interestingly 2 (0.5%) patients with urticaria and 1 (1.1%) with urticaria-angioedema received adrenaline. Diagnostic uncertainty emerged from post-hoc re-evaluation of these three cases, due to the presence of clinical features (airway involvement) which may be consistent with a diagnosis of anaphylaxis. The triggers in the five

patients with anaphylaxis who were treated with adrenaline were oral levofloxacin (n=1), intramuscular ceftriaxone (n=1), oral ketoprofen (n=1), whereas no specific cause could be established for the remaining two cases. The complete report of treatments administered in each group is shown in table 2. Only three patients with anaphylaxis needed hospitalization, all for the presence of severe comorbidities (a 31 year old woman affected by Cornelia de Lange syndrome, with multiple organ failure; an 85 year old woman with diabetes, coronary artery disease and arterial hypertension; a 77 year old man, with severe chronic obstructive pulmonary disease). Most cases were managed in the ED Observation Unit (EDOU) for 12-24 hours. Importantly, no death and no Intensive care unit (ICU) admission was recorded within 1 month from ED admission for the acute allergic episode.

## Discussion

The results of our study show that anaphylaxis is widely undertreated with adrenaline in our local ED compared to current guidelines and recommendations, and this is in agreement with previous reports. (11,14-17)

The significant diagnostic uncertainty is indeed one of the leading problems for diagnosing and treating anaphylaxis. An international and interdisciplinary group of experts attempted to establish clinical criteria for increasing the accuracy in diagnosing anaphylaxis during the US National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA) and the Food Allergy and Anaphylaxis Network (Chantilly, VA, USA) convened symposia. (5) The adopted working definition was as follows: “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death”. The group also proposed that anaphylaxis is likely to be clinically present if any one of three major criteria is satisfied within minutes to hours: (i) acute onset of illness with involvement of skin, mucosal surface, or both, and at least one of the following: respiratory compromise, hypotension, or end-organ dysfunction; (ii) two or more of the following occur rapidly after exposure to a likely allergen:

involvement of skin or mucosal surface, respiratory compromise, hypotension, or persistent gastrointestinal symptoms; and (iii) hypotension develops after exposure to a known allergen for that patient: age-specific low blood pressure or decline of systolic blood pressure of >30% compared to baseline. (5) The group concluded that these criteria “are likely to capture more than 95% of cases of anaphylaxis”. However, the report also states that “There undoubtedly will be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near-fatal anaphylaxis to peanut who ingested peanut and within minutes is experiencing urticaria and generalized flushing. Since anaphylaxis occurs as part of a clinical continuum, occasionally beginning with relatively modest symptoms and then rapidly progressing to a life-threatening condition, the delay of treatment up to development of multi-organ symptoms must be considered a tangible risk. Therefore, some of the authors and Committee members of the WAO Ad Hoc Committee on Epinephrine and Anaphylaxis recommended that any symptoms of anaphylaxis, such as generalized pruritus, erythema, urticaria, and angioedema alone, and any other systemic symptom including those not involving vital organs, should be treated immediately (and as necessary) with appropriate i.m. doses of epinephrine in an attempt to prevent the occurrence of more severe systemic consequences. Notably, this statement is not evidence-based, since no single study has shown that this clinical management produces effective prevention towards systemic involvement.

Skin involvement, occurring in up to 80-90% patients with anaphylaxis, (18) is a possible confounding factor, which creates some degree of overlap with severe and refractory urticaria. The recent European Guidelines for anaphylaxis (10) recommend adrenaline administration in the presence of cardiovascular or multisystemic involvement, but the use of this practice has a lower strength of recommendation (i.e., C and D) in patients with limited respiratory, gastrointestinal or skin involvement. This is mainly attributable to the fact that solid evidence is available for the most severe clinical presentation of anaphylaxis, like hymenoptera

sting. (19)

In our study, the percentage of unknown triggers for anaphylaxis was 19.6%, which is in agreement with that reported in the recent literature (i.e., 20%). (20) As regards adrenaline administration, one large case series published by an Italian centre reported that the percentage of patients treated with this drug was 5.9%, slightly lower than in our study (i.e., 8.9%), thus confirming the evidence of a generalized underuse of epinephrine in this clinical setting. (15)

No prospective human studies have been published so far about the optimal management of anaphylaxis with adrenaline, nor is information available on dosage and bioavailability of i.m. adrenaline, when used in this condition. Even more importantly, the incidence of adverse effects after adrenaline administration in patients with anaphylactic reactions remains uncertain. Some case reports and mortality reviews suggest that a number of side-effects (especially those involving the myocardium) can occur, are globally severe and more frequently observed in patients with inappropriate drug dosage (i.e., overdose, or an overly rapid rate of infusion). (21) There is also increasing awareness that the heart may be a target organ in anaphylaxis, and that electrocardiographic changes suggestive of ischemia, myocardial infarction or dysrhythmias may occur even in patients not receiving adrenaline. (22-25) Interestingly, only the i.v. route of administration was used in two published human studies, showing a favorable effect in patients with allergic reactions accompanied by cardiovascular collapse. (26)

A recent Cochrane review on adrenaline as a treatment of anaphylaxis failed to report any evidence from prospective, randomized or quasi-randomized trials on the effectiveness of this drug for emergency management of anaphylaxis. (27) This lack of evidence was mainly attributed to the relative infrequency of severe anaphylactic reactions, the rapid onset, the often unexpected occurrence, as well as by the widely accepted role of adrenaline in various clinical settings. (13,27)

In conclusion, the results of our study suggest that anaphylaxis seems to



be widely undertreated with adrenaline in our local ED compared to existing guidelines and recommendations, and this is in agreement with previous reports. (11,14-17) Nevertheless, a favorable outcome was recorded for all patients included in this study, even when managed with second- and third-line treatments. In fact, no death was observed at 1 month and the number of hospitalizations was very limited (3/589; 0.5%), mainly due to comorbidities rather than to treatment failure. We hence assume that these findings should be addressed as food for thought for reconsidering the validity of recommendations contained in current guidelines.

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**Urticaria- All cases**

	<b>Anaphylaxis</b>	<b>Urticaria</b>	<b>Angioedema</b>	<b>angioedema</b>	<b>n</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>(%)</b>
<b>Drugs</b>	18 (32.1)	67 (18.4)	13 (17.3)	22 (23.1)	129 (21.9)
<b>Food</b>	17 (30.3)	52 (14.3)	6 (8)	14 (14.7)	88 (15.0)
<b>Hymenoptera sting</b>	5 (8.9)	29 (8.0)	12 (16.0)	11 (11.6)	58 (9.9)
<b>Chemicals</b>	5 (8.9)	16 (4.4)	3 (4)	11 (11.6)	26 (4.4)
<b>Unknown</b>	11 (19.6)	199 (54.8)	41 (54.6)	37 (38.9)	288 (48.9)

**Table 1.** Triggers for allergic-anaphylactic episodes, subdivided according to type of reaction.

	<b>Anaphylaxis</b>	<b>Urticaria</b>	<b>Angioedema</b>	<b>Urticaria- angioedema</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<b>Adrenaline</b>	5 (8.9)	2 (0.5)	0	1 (1.1)
<b>Methylprednisolone</b>	40 (71.4)	261 (71.9)	58 (77.3)	78 (82.1)
<b>Chlorfenamine</b>	35 (62.5)	277 (76.3)	53 (70.7)	84 (88.4)
<b>Ranitidine</b>	32 (57.1)	125 (34.4)	24 (32.0)	33 (34.7)
<b>Others</b>	24 (42.9)	15 (4.1)	3 (4.0)	6 (6.3)

**Table 2.** Pharmacologic treatments given in the Emergency Department for different types of allergic episodes. The term “others” refers to: oxygen, salbutamol, crystalloids.

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