

Profile of serious angioedema requiring an urgent advice from a national reference call center

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Abstract

Angioedema (AE) is a reason for emergency care when it is severe. Care is difficult when the diagnostic is not known before the attack: mast cell (MC) or bradykinin (BK) mediated. One is very common but often benign, the other rare but potentially fatal. The French national reference center of angioedema (CREAK) provides emergency physicians with a hotline and a guideline to help them manage their patients. This study aimed to describe the clinical features of AE episodes prompting a call on the CREAK hotline and classify patients depending on the suspected cause of the AE. This is a retrospective study between March and August 2019. Each physician calling on the CREAK hotline was asked to fill a clinical description form for the AE emergency. Known patients of CREAK was excluded. Eighty four patients were included. Forty one (48.8%) in the angiotensin converting enzyme inhibitors induced acquired angioedema (ACEi-AAE), 39 (46.4%) in the mast cell induced angioedema, and 4 (4.8%) in the Bradykinin mediated angioedema. The mast cell induced angioedema patients have more history of hives (29.3%) than ACEi-AAE (2.4%, $P=.0004$). ACEi-AAE mainly affected the tongue (58.5% vs 25.6%, $P=.003$) and larynx (29.3% vs 13%, $P=.001$). In 65.5% of cases, the etiological diagnosis was not mentioned by the appellant, but made by the hotline. In 31% of cases, the hotline suggested the administration of a specific treatment not previously provided by the caller. All the doctors who called the hotline appreciate this tele-expertise especially in case of ACEi-AAE presumptions. In addition to providing rapid AE expertise, this service also allows to educate physicians in the management of AE irrespective of its origin.

Abbreviations: ACEi = angiotensin converting enzyme inhibitors, ACEi-AAE = angiotensin converting enzyme inhibitors acquired angioedema, AE = angioedema, BK-AE = bradykinin mediated angioedema, CREAK = National reference center for angioedema, ED = emergency department, ENT = ear, nose, and throat, ICU = intensive care unit, MC-AE = mast cell induced angioedema.

Keywords: angioedema, angiotensin converting enzyme inhibitors, hotline

1. Introduction

Angioedema (AE) is defined by a sudden, localized swelling of the mucous membranes and the deep layers of the skin that regress over hours or days. It is caused by vascular leakage induced by vasoactive substances. It can affect any part of the body, but often affects the eyelids, lips, hands, feet, genitals, and the respiratory and digestive tracts. It may be associated with hives. Angioedema accounts for about 114,000 emergency department (ED) visits per year in USA.^[1] Data from Italy suggest that 0.37% of all ED visits are related to angioedema and Canadian study estimated that 1:1000 ED visits are angioedema related.^[2,3] Isolated AE are classified depending on their causal vasoactive mediator. Thus, 2 broad categories of AE are identified: mast cell induced angioedema (MC-AE) and bradykinin mediated AE (BK-AE).^[4] Histamine is the main mediator of MC-AE. MC-AE are mainly spontaneous and look like spontaneous urticarial.^[5] Sometimes, they are associated with non-steroid anti-inflammatory drugs. Isolated MC-AE are rarely the symptoms of anaphylaxis.

Allergic AEs are often associated with digestive and respiratory signs, diffuse erythema, and shock. BK-AE can be associated with C1inhibitor (C1Inh) deficiency (hereditary or acquired) but the most frequent are angiotensin converting enzyme inhibitors (ACEi) induced AE. It affects 0.7% of ACEi users. In France, we have estimated that it represents 5000 patients a year.^[6,7]

In ED, patients referred for a serious AE (face or respiratory tract) are a diagnosis and therapeutic challenge. BK-AE may be lethal, and require specific, onerous treatments, with limited availability, while MC-AE (with the exception of anaphylaxis) is exceptionally fatal and very common. Thus, BK-AE has a 45-fold higher mortality risk than MC-AE.^[8] Often patient cannot speak because of the larynx localization of angioedema.^[9] It is impossible to conduct a detailed interrogation. Physicians must treat quickly the patient without waiting for the results of laboratory tests.

In 2011, French national reference center for angioedema (CREAK) created a national tele-assistance for known patients with HAE. Then, in a second step, this hotline was available

I. Boccon-Gibod and L. Bouillet received research grants and consulting fees from Takeda, Behring, Pharvaris, Kalvista.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Simon N, Bocquet A, Boccon-Gibod I, Bouillet L. Profile of serious angioedema requiring an urgent advice from a national reference call center. *Medicine*. 2022;101:31(e29513).

Received: 22 July 2021 / Received in final form: 5 April 2022 / Accepted: 14 April 2022

<http://dx.doi.org/10.1097/MD.00000000000029513>

for all French emergency doctors to help them with diagnostic and therapeutic management of AE. This call center is available 24hours a day and concerns all types of angioedema. The CREAK created and distributed a guideline for the management of AE in emergencies with the phone number (posters in doctors' offices) (Fig. 1). This study aimed to describe the clinical features of AE episodes prompting a call on the national AE hotline.

2. Methods

We have done a retrospective study from March 1, 2019 to July 31, 2019. Every physician that called the national CREAK hotline was asked to fill a form with clinical data concerning the AE episode prompting the call. The collected data was the age, sex, personal or familial history of AE or urticaria, the location of the AE, the duration of the episode, treatments administered before the call, and the final diagnosis. In case of missing information, patients were directly contacted if they had given their consent to a follow up call. Calls concerning known patients of the CREAK were excluded. A local ethics committee approved the study protocol. According to French legislation, no written informed consent of patients was required.

Quantitative variables were expressed as means and standard deviations if normally distributed (as determined by Shapiro-Wilk), otherwise they were expressed as median and range (25th–75th percentile). Qualitative variables were expressed as percentages.

Quantitative variables were compared by Kruskal–Wallis or Student *t* test. Qualitative variables were compared by Fisher exact test or Chi-square test. Results were considered statistically significant for a *P*-value inferior to .05.

One hundred thirty five calls were made during the study. Thirty three concerned known patients of the CREAK. Two calls concerned the same patient, the second call was not included. Seventeen calls were excluded due to lacking clinical information. A total of 84 calls were therefore finally investigated.

3. Results

The characteristics of the study population are summarized in Table 1. The duration of the AE episode was under 24hours in

48 patients (57.1%), from 24 to 72hours in 21 patients (25%), and over 72hours for 9 patients (10.7%). Eighty three patients had AE, 17 had AE associated with hives, and 1 patient had isolated hives.

AE affected the face in 55 patients (65.5%), the tongue in 36 patients (42.9%), ear, nose, and throat (ENT) in 19 patients (22.6%), extremities in 7 patients (8.3%), and 3 patients complained of abdominal pain (3.6%) (Table 1). Twenty nine patients had several simultaneous locations of AE (34.5%). In 65.5% of cases, the etiological diagnosis was not mentioned by the appellant, but made by the hotline. The diagnostic assumptions were 49% of angiotensin converting enzyme inhibitors acquired angioedema (ACEi-AAE), 46.3% of MC-AE, and 4.7% of BK-AE.

Eighty patients received antihistamines (95.2%), 44 steroids (52.4%), 15 adrenalin (17.9%, 13 by inhalation, 2 intravenously), 17 received Icatibant (20.2%), 5 received human C1 inhibitor (6%). Nine patients were transferred to an intensive care unit, 2 of which were intubated. In 31% of cases, the hotline suggested the administration of a specific treatment not previously provided by the caller (mainly icatibant).

3.1. BK-AE

Four patients had a BK-AE (4.7%) of which 1 by the hotline, 3 female and 1 male. The median age in this group was 28years (8–53.5). Two had prior history of AE (50%), none had a priori history of hives. No patients were treated by ACEi or ARB. None reported familial history of AE. The duration of the AE episode was between 24 and 72hours in 2 patients (50%) and over 72hours in 2 patients (50%). The 4 patients had no hives. The AE was located at the face in 2 patients (50%), ENT in 2 patients (50%). Two patients (50%) had several simultaneous locations of AE. Administered treatments at the time of call were antihistamines for 4 patients (100%), steroids for 1 patient (25%), intravenous adrenaline for 1 patients (25%), and 3 patients received Icatibant or C1 inhibitor. One patient was intubated in the intensive care unit (ICU). The administration of icatibant was recommended for this patient by the hotline.

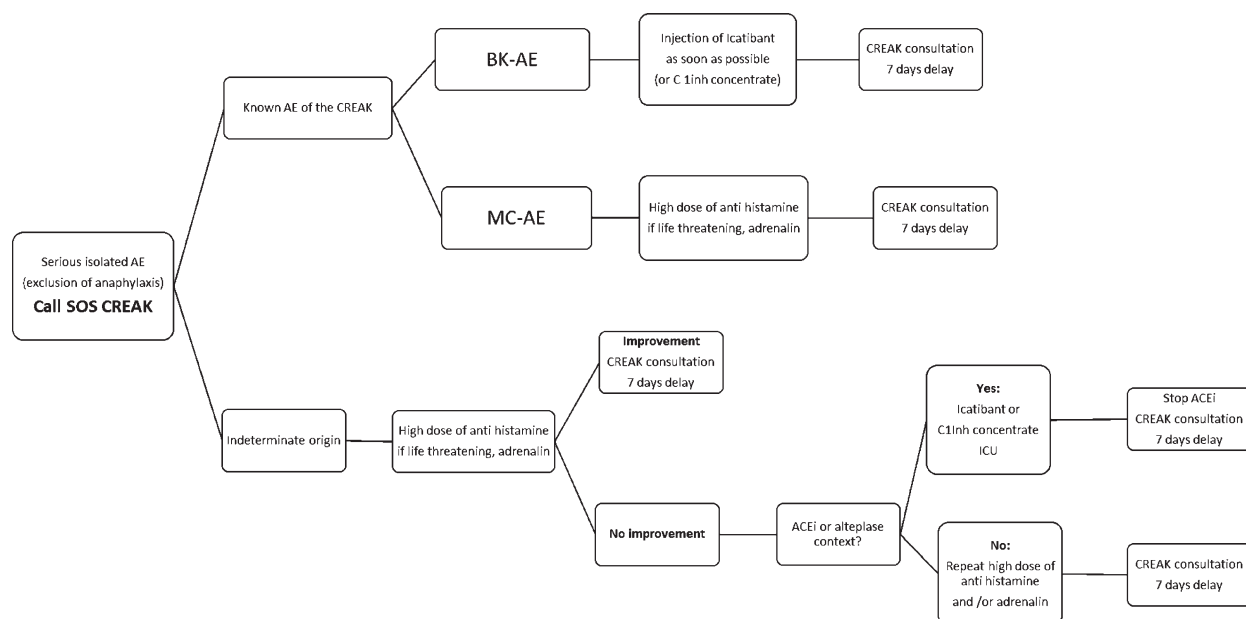


Figure 1. Guideline for the management of AE in emergencies. ACEi=angiotensin converting enzyme inhibitors, BK-AE=bradykinin mediated angioedema, CREAK=French national reference center for angioedema, MC-AE=mast cell induced angioedema.

Table 1
Differences in clinical profiles of angioedema.

	Total	MC-AE presumption	ACEi-AE presumption	P
N (%)	84	39 (46.4%)	41 (49%)	na
Sexe ratio F/H	1	1.1	0.7	0.37
Age (median), yrs	59 (39–69.5)	40.5 (28–58)	69 (62–75)	<0.00001
History of				
AE	45 (53.6%)	21 (54%)	22 (53.7%)	0.92
Hives	13 (15.5%)	12 (29.3%)	1 (2.4%)	0.0004
ACEi	45 (51%)	4 (10.3%)	41 (100%)	na
Episode duration				
24–72 h	48 (57%)	24 (61.5%)	24 (58.5%)	0.64
>72 h	21 (25%)	7 (18%)	12 (29.3%)	0.26
>72 h	9 (10.7%)	5 (13%)	3 (7.3%)	0.47
AE location				
Face	55 (65.5%)	31 (79.5%)	22 (53.7%)	0.015
Tongue	36 (43%)	10 (25.6%)	24 (58.5%)	0.003
ENT	19 (22.6%)	5 (13%)	19 (29.3%)	0.001
Extremities	7 (8.3%)	6 (15.4%)	1 (2.4%)	0.054
Multiple locations	29 (34.5%)	12 (31%)	15 (36.6%)	0.58
Abdominal pain	3 (3.6%)	2 (5%)	1 (2.4%)	0.61
Concomitant hives	3 (3.6%)	17 (43.6%)	0	na
Treatments:				
Anti histamine	80 (95%)	39 (100%)	37 (90%)	0.11
Steroids	44 (52.4%)	19 (48.7%)	24 (58.5%)	0.38
Adrenalin	15 (18%)	6 (15.4%)	8 (19.5%)	0.63
Icatibant/C1Inh	22 (26%)	0	19 (46.3%)	na
ICU transfert	9 (10.7%)	1 (2.6%)	7 (17%)	0.057

ACEi-AE=angiotensin converting enzyme inhibitors induced angioedema, ICU=intensive care unit, MC-AE=mast cell induced angioedema.

3.2. ACEi-AAE

An ACEi-AAE was diagnosed for 41 patients of which 43.6% by the hotline (Table 1). The median age in this group was 69 years (62–75). Twenty two had had at least 1 episode of AE prior to the call (53.7%). The duration of the AE episode was <24 hours in 24 patients (58.5%), between 24 and 72 hours in 12 patients (29.3%), and over 72 hours in only 3 patients (7.3%).

The AE was located at the tongue in 24 patients (58.5% of the ACEi-AAE), the face in 22 patients (53.7%), the ENT in 19 patients (29.3%), the extremities in 1 patient (2.4%), and 1 patient had abdominal pain associated with AE of the face (2.4%). Fifteen patients (36.6%) had several simultaneous locations of AE.

Administered treatments at the time of call were antihistamines for 37 patients (90.2%), steroids for 24 patients (58.5%), adrenaline for 8 patients (19.5%, 7 by inhalation, 1 intravenously), and Icatibant or human C1 inhibitor for 19 patients (46.4%). Seven patients (17.1%) were transferred to an intensive care unit. The administration of icatibant or human C1 inhibitor was recommended for 61% patients by the hotline.

3.3. MC-AE

Thirty nine patients had a MC-AE. The etiology of MC-AE was identified by the hotline in 89.7% of cases: 4 were allergic, 2 were induced by non-steroid anti-inflammatory drug, and 33 were spontaneous (Table 1). The median age in this group was 40.5 years (28–57.8). Twenty one had prior history of AE (53.9% of the MC-AE group), 12 patients (29.3%) had prior history of hives. Four patients were treated by ACEi (but were classified in this group due to the presence of hives during the AE episode). The duration of the AE episode was <24 hours in 24 patients (61.5%), between 24 and 72 hours in 7 patients (18%), and over 72 hours in 5 patients (12.8%).

During the episode prompting the call, 17 had AE and hives (43.6%), only one patient having only hives. The AE was located at the face in 31 patients (79.5%), tongue in 10 patients (25.6%), extremities in 6 patients (15.4%), ENT in 5 patients

(12.8%), and 2 patients had abdominal pain during the episode (5.1%). Twelve patients (30.8%) had several simultaneous locations of AE.

Administered treatments at the time of call were antihistamines for 39 patients (100%), steroids for 19 patients (58.5%), inhaled adrenaline for 6 patients (15.4%). One patient was transferred to an ICU without intubation. No patients were treated by Icatibant or C1 inhibitor.

3.4. Comparison between ACEi-AAE and MC-AE

The MC-AE patients have more history of hives than ACEi-AAE: 29.3% versus 2.4%, $P=0.0004$. The ACEi-AAE patients are older: 69 (28–58) versus 40.5 (62–75) years, $P<0.00001$. ACEi-AAE mainly affected the tongue and ENT: 58.5% versus 25.6%, $P=0.003$ and 29.3% versus 13%, $P=0.001$. ACEi-AAE are more transferred to intensive care units: 17% versus 2.6%, $P=0.057$.

3.5. Caller origin

Fifty six calls were made from an ED (66.6%), 11 from an ICU (13.1%), 7 from an inpatient facility (8.3%: 4 from internal medicine wards, 1 from a hematology, dermatology, and pediatric ward), 6 from outpatient family physicians' practices, 4 from an unknown location (Fig. 1). Forty eight calls were made from a general hospital (57.1%), 26 from a teaching hospital (30.9%), and 6 from private practice offices.

4. Discussion

In an Italian tertiary center, Zingale et al^[10] reported that 49% of isolated AE (without hives) were mast cell mediated (16% were allergy related and 33% idiopathic), 36% were bradykinin induced (25% with C1 inhibitor deficiency, 11% drug related). Another study from a specialized AE center reported that 70% of AE without hives were mast cell mediated.^[11] The distribution of

our study is a little different. It can be explained by the different method of patient recruitment. The emergency doctors who called the hotline, did it for the most serious AE and/or the most difficult diagnosis but also when the first line of treatment failed. We have not studied the calls of known patients of the CREAK (33 calls).

The hotline provided significant diagnostic and therapeutic assistance, especially for the diagnosis and treatment of ACEi-AAE. This study highlights the importance of ACEi-AAE in ED (49% of the calls). This diagnosis is very difficult to do. There was no statistically significant difference in the length of the episodes between the groups even if mast cell mediated AE are considered to be shorter than bradykinin mediated AE.^[12,13] This may be explained by our measure of the episode length, only differentiating episodes under 24 hours, between 24 and 72 hours and over 72 hours. ACEi-AAE patients had statistically more AE localized to the tongue than patients in the MC-AE group, and less AE localized to the face. It is to be noted that almost every episode in this study concerned the face, tongue or ENT, and AE of the extremities or abdominal pain were almost inexistent, even if they are associated with mast cell and bradykinin mediated AE.^[12,13] This may be explained by the identity of callers: almost 80% of calls originated from an ER or ICU, most patients with AE of the extremities or with abdominal pain will be considered less severe or may not even seek medical care. Only 4 patients in this study had no AE of the face-tongue or larynx. These patients had more frequent tongue and larynx localizations compared with MC-AE. Seven ACEi-AAE patients versus 1 MC-AE were transferred to an ICU. Two hypotheses can be discussed: emergency doctors used our guideline well and transfer suspicions of ACEi-AAE to ICUs as recommended (Fig. 1). Or, ACEi-AAE are really more severe and required ICU as it has been shown before by Javaud et al.^[14] In the absence of clinical signs or paraclinical tests to help differentiate MC-AE versus ACEi-AAE, and considering the potential severity of BK-AE, the use of specific treatments (i.e., Icatibant or C1Inh concentrate) remains necessary, even though some of the patients merely present with MC-AE while under treatment by an ACEi.^[15,16] Thus in 30% of cases, the hotline offered a specific treatment not yet prescribed by the caller. This was mainly in the case of ACEi-AAE. This shows the usefulness of the hotline on patient care in the emergency room.

In the case of MC-AE, the hotline mainly allowed an etiological diagnosis and help in the elimination of an allergic cause. When faced with AE, emergency physicians first think of a diagnosis of anaphylaxis. However, in case of isolated AE (without other clinical sign), the diagnosis of allergy is very unlikely. The hotline makes it possible to eliminate this diagnosis, and thus to reassure the patient. And sometimes to avoid therapeutic escalation.

5. Limitations

It is a retrospective study and the data may be missing. Thus, statistical analyzes should be taken with caution. We can have overestimated the number of ACEi-AAE, because the diagnosis is very difficult. A recurrence of AE after 6 months of ACEi stop is not very in favor of an ACEi-AAE especially if hives occur. The final diagnosis of ACEi-AAE must be done after 6 months to evaluate the AE incidence after the cessation of ACEi. The persistence of AE 6 months after, would reclassify patients to spontaneous MC-AE.^[16] We did not have this 6-month follow-up for patients.

6. Conclusion

All the doctors who called the hotline appreciate this tele-expertise a lot. In addition to providing rapid AE expertise, to correcting the diagnosis, and sometimes to offer a specific treatment, this service also allows to educate physicians in the management of AE irrespective of its origin.

6.1. Uncited references

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Visualization: Alexis Bocquet.

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