Bradykinin-mediated angioedema: factors associated with admission to an intensive care unit, a multicenter study
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Objective Bradykinin-mediated angioedema is characterized by transient attacks of localized edema of subcutaneous or submucosal tissues and can be life-threatening when involving the upper airways. The aim of this study was to determine the features of acute attacks that might be associated with admission to an ICU.

Patients and methods We carried out a retrospective, multicenter, observational study in consecutive patients attending one of six reference centers in France for acute bradykinin-mediated angioedema attacks. Patients had been hospitalized for an acute episode at least once previously. Acute attacks requiring ICU admission were compared with acute attacks that had not required ICU admission.

Results Overall, 118 acute attacks in 31 patients were analyzed (10 patients with hereditary angioedema, 19 patients with angiotensin-converting enzyme inhibitor-induced angioedema, and two patients with acquired C1-inhibitor deficiency angioedema). In multivariate analysis, upper airway involvement, corticosteroid, and C1-inhibitor concentrate administration were associated with ICU admission. Seven episodes (18%) needed airway protection. The evolution was favorable in 38 of 39 attacks warranting ICU admission: patients were able to get out of the service (mean ICU stay 4 ± 5 days). One death was observed by asphyxiation because of laryngeal swelling.

Conclusion Upper airway involvement is an independent risk factor for ICU admission. Corticosteroid use, which is an ineffective treatment, and C1-inhibitor concentrate use are factors for ICU admission. The presence of upper airway involvement should be a warning signal that the attack may be severe. European Journal of Emergency Medicine 23:219–223 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction
Bradykinin-mediated angioedema (BK-AE) is characterized by transient attacks of localized edema of subcutaneous or submucosal tissues [1–3]. It can be life-threatening when it involves the upper airways. Hereditary angioedema (HAE) may be associated with C1-inhibitor (C1-inh) deficiency (type I and II) or not (HAE with normal C1-inh) [4]. Acquired angioedema (AE) is either drug-induced by angiotensin-converting enzyme inhibitors (ACE-Is) or because of C1-inh deficiency [5,6]. In the absence of emergency-specific treatment to BK-AE, the mortality rate of laryngeal edema is 25% [7]. Painful abdominal attacks can also be severe when they cause bowel subocclusion or, less commonly, hypovolemic shock [8,9]. Management of severe BK-AE attacks (abdominal, face, or upper airways) requires early administration of either icatibant or C1-inh concentrate [4,10,11].

Acute attacks may prompt admission to an ICU for treatment and surveillance, as observed in 5% of HAE and in 11% of ACE-I AE in two retrospective studies [1,2]. The aim of the present study was to determine the features of acute attacks that are associated with ICU admission.

Patients and methods
Patients and setting This was a retrospective study of consecutive BK-AE patients who attended one of six reference centers for
BK-AE in France between January 2002 and January 2012 (Bondy, Lyon, Grenoble, Angers, Clermont-Ferrand, and Caen). Our study complies with STROBE guidelines for observational studies [12].

Inclusion criteria were documented HAE [4,11,13,14] (type I, II, or with normal C1-inh), ACE-I-induced AE [5,15] or AE because of acquired C1-inh deficiency [3,6]. Patients were followed in reference centers of the study. At least one crisis led in ICU. The only noninclusion criterion was age younger than 18 years. The study protocol was approved by the ethics committee. No consent was needed in accordance with French law.

Data collection and analysis
A physician with experience in BK-AE, but unaware of the study objective, was in charge of retrospective patient inclusion. He gathered the following data: (i) clinical data: sex, age, AE type, personal and family medical history of AE, attack frequency and sites (abdomen, face, larynx), any long-term treatment, and treatment administered for attack; (ii) biological data: antigenic and functional levels of C1-inh, C4, and C1q; and (iii) genetic data: mutations of the SERPING1 gene for types I and II HAE and mutation of the F12 gene for HAE with normal C1-inh. The principal investigator verified the database.

Acute attacks requiring ICU admission were compared with acute attacks not requiring ICU admission.

Statistical analyses
Quantitative variables are described as medians with interquartile ranges (IQRs) and categorical data as numbers with percentages. Variables associated with ICU admission were identified using a logistic regression model. This logistic regression model based on generalized estimating equations was used to account for patients who had multiple attendances. A stepwise multivariate analysis was carried out with sex, age, type of attack, and treatment as candidate variables. All tests were two-sided. A P value less than 0.05 was considered significant. We used R statistical software (version 2.15.2; R Foundation for Statistical Computing, Vienna, Austria).

Results
Patient characteristics
A total of 118 attacks in 31 patients were analyzed, of which 39 (33%) resulted in ICU admission. Patient characteristics are presented in Table 1. There were 16 men and 15 women. Patients admitted to the ICU with ACE-I-induced AE were significantly older than those with HAE [median age: 74 (IQR 63–76) vs. 34 (IQR 30–38) years; P < 0.001]. Patients with acquired C1-inh deficiency were also older than those with HAE. This difference was not significant [76 (71–81) vs. 34 (30–38) years; P = 0.06].

| Table 1 Patient characteristics | Patients (n=31) |
|--------------------------------|----------------|
| Male [n (%)]                  | 16 (52)        |
| Median age (IQR) (years)      | 66 (40–76)     |
| Type of angioedema [n (%)]    |                |
| Hereditary type I             | 5 (16)         |
| Hereditary type II            | 3 (10)         |
| Hereditary type III           | 2 (6)          |
| Acquired C1-inh deficiency    | 2 (6)          |
| Drug-induced (ACE inhibitor)  | 19 (62)        |
| Long-term treatment [n (%)]   |                |
| Danazol                      | 6 (19)         |
| Tranexamic acid              | 3 (10)         |
| C1-inh concentrate           | 0 (0)          |

Nineteen patients had ACE-I-induced AE because of one of the following drugs: perindopril (n = 11), ramipril (n = 2), enalapril (n = 2), benazepril (n = 2), trandolapril (n = 1), and lisinopril (n = 1). The median interval between the start of treatment and the first AE attack was 3 months (IQR 2.5–32.5). The attacks before the diagnosis did not require hospitalization.

Ten patients had HAE. Patients with HAE with normal C1-inh had a mutation of the F12 gene. Patients with acquired C1-inh AE had a non-Hodgkin’s lymphoma. A large majority of patients with HAE were on danazol or tranexamic acid at the time of ICU admission. No patient with HAE was receiving C1-inh prophylaxis.

Acute attacks and intensive care unit admission
In univariate analysis, ICU admission was significantly more likely in patients with ACE-I-induced AE attacks [odds ratio (OR) = 4.98], but significantly less likely in patients with acquired C1-inh deficiency (OR = 0.15) (Table 2). ICU admission was less likely in cases of acute HAE attacks, but not significantly so (OR = 0.58). ICU admission was significantly more likely for upper airway attacks (OR = 20.6), but not for abdominal (OR = 1.35) or facial (OR = 1.80) attacks.

Laryngeal involvement was present in 30/39 (77%) acute attacks, which prompted ICU admission (Table 2). Laryngeal involvement was present in 20/36 (56%) of ACE-I-induced attacks and in 20/59 (34%) of attacks in HAE patients (Table 2). Macroglossia was present in 25/36 (69%) of ACE-I-induced attacks. Seven of the 30 (23%) laryngeal attacks prompting ICU admission required airway protection [otracheal intubation (n = 2), tracheotomy (n = 3), or intubation, followed by tracheotomy (n = 2) because of a long ventilator weaning for aspiration pneumonia]. Five of the attacks with airway protection were because of ACE-I. Involvement of the face was present in 16/39 (41%) acute attacks, prompting ICU admission. Twenty-two attacks prompting ICU admission were multisites. Laryngeal involvement was present in 16/22 (77%) of multisite attacks and in 13/17 (77%) of unisite attacks.
Administration of BK-AE-specific treatments (C1-inh concentrate or icatibant) for severe attacks of the face, abdominal, or upper airways, as well as of unpecific treatments (corticosteroids, antihistamines, and epinephrine) was significantly more common in the case of attacks warranting ICU admission (Table 2). Specific treatment (icatibant or C1-inh concentrate) was used in 41 (35%) attacks. This treatment was administered in 28/41 (72%) cases either in the ICU (14 cases) or before admission to the ICU (10 in the ED and four in the ambulance), and in 13/41 (16%) cases not requiring ICU admission (P < 0.001). Fresh-frozen plasma was not used to treat attacks in French centers. The course of the attacks was favorable in 38 of the 39 attacks prompting ICU admission, with a mean ICU stay of 4 ± 5 days. A patient with HAE died on day 8 in the ICU after an anoxic brain injury secondary to asphyxiation from laryngeal involvement.

In a multivariate logistic regression model, upper airway involvement and C1-inh concentrate use were associated independently with an eight-fold higher likelihood of admission to the ICU, and corticosteroid use was associated with a seven-fold higher likelihood (Table 3). Acquired C1-inh deficiency was associated with a five-fold lower likelihood.

**Discussion**

The main independent risk factors associated with ICU admission for a BK-AE attack were upper airway involvement as well as treatment by corticosteroids. Administration of C1-inh concentrate was associated with an eight-fold higher likelihood of ICU admission than icatibant, probably because it is a marker of attack severity. Indeed, attacks hospitalized in ICU required peripheral venous access for the emergency symptomatic treatment. It can include hypnotic and paralytic drug for airway protection, resuscitation fluids for hypovolemic shock associated with abdominals attacks, and antalgic use for pain. Given the fact that the ICU patients are perfused, C1-inh concentrate use seems to be more logical, given its intravenous route of administration. Icatibant is administered subcutaneously. However, this difference in use does not seem justified, given the effectiveness of two treatments in efficacy studies [10,16]. Corticosteroid use was associated with a seven-fold higher likelihood of ICU admission. Its administration in the ED to patients with AE is usual [16] because of the high frequency of histaminic AE. This first step is logical, given the diagnostic uncertainty, but corticosteroids are ineffective and inappropriate in BK-AE and can delay specific management [11]. This delay may explain the higher likelihood of ICU admission, but this has not been investigated. Early access to specific treatments is a challenge for emergency (prehospital and intrahospital) medicine. It must be readily available as early treatment can be life saving. ACE-I-induced attacks were not an independent risk factor for ICU admission, even though most ICU admissions were prompted by ACE-I-induced attacks. The frequent upper airway involvement in these cases (56% in our study) can explain ICU admission [1,5,17,18].
Attack of the upper airways (laryngeal swelling and/or macroglossia) was associated with an eight-fold higher likelihood of ICU admission \[OR = 8.4 (1.2–48.5)\]. The presence of these factors predicts clinical course and ICU admission. This was not an unexpected result as we have already shown that laryngeal swelling increases the likelihood of a visit to a hospital ED [19], implying a higher probability of ICU admission and of morbidity and mortality.

Laryngeal swelling was present in 77\% of acute attacks, prompting ICU admission. The incidence was 56\% for ACE-I-induced attacks (whether prompting ICU admission or not), which is at the higher end of the published range in recent retrospective studies (2–59\%) [1,17,18,20], and 34\% for HAE attacks, which is well above the 4\% reported in a large-scale prospective study [21]. However, our study selected patients with more severe involvement. ACE-I AE involves upper airways in a high frequency. ACE-I AE is a risk factor for ICU admission. The need for airway protection for laryngeal swelling in ACE-I-induced attacks was also higher than reported so far (2–7\%) [2].

These previous studies described patients of the ED. Our study selected patients in the ED and those who go at least once to ICU. Thus, they selected patients with less severe involvement. We encountered one fatality from asphyxiation. At the time of attack requiring ICU hospitalization, the patient had received no long-term treatment. In addition, the emergency-specific treatment was delivered too late. Laryngeal swelling in BK-AE patients must be a warning signal because it can cause death [22]. In this study, the diagnosis improves the therapeutic management even if access to specific treatment is a challenge for the patients [22].

The incidence of macroglossia in our patients (69\% of patients) with ACE-I-induced attacks was also higher than reported so far (22–52\%) because of the high frequency of ACE-I AE in our study [1,17,18,20]. Macroglossia is a typical involvement of the ACE-I AE. It can be complete or may involve a hemitongue. If untreated, macroglossia can impede intubation and lead to death by mechanical obstruction of the upper airways [23].

Abdominal attacks accounted for 15\% of all attacks. Such attacks resulted in hemodynamic failure only in the case of 1\% of attacks compared with a reported incidence of 4\% of attacks in HAE patients [8].

Appropriate specific treatment for BK-AE (C1-inh concentrate or icatibant) was administered for 28 (72\%) attacks prompting ICU admission, but the treatment was administered before ICU admission in only half of these attacks. The involvement of the face should be treated to avoid an unfavorable course and ICU admission. Other clinical criteria to treat an attack are an involvement of the upper airway and/or abdominal attacks. Early management thus needs to be improved, with better availability of specific treatments [24].

**Limitations**

The main limitations of our study were its retrospective design and small patient numbers. Even though data collection was standardized, a certain number of factors, such as time to attacks management, were not documented.

**Conclusion**

Factors associated with ICU admission in patients who had already been admitted at least once to an ICU for an acute episode of BK-AE were upper airway attack (laryngeal swelling and/or macroglossia). Corticosteroid use, which is an ineffective treatment, is also a factor for ICU admission. Its administration in the ED to patients with AE is usual because of the high frequency of histaminic AE. Resistance to corticosteroid treatment is directed towards the diagnosis of BK-AE. The presence of any of these factors should be a warning signal that the attack may be severe. When a patient presents with laryngeal edema, examination research an ACE-I. The high number of AE in emergency conditions emphasizes the need for an effective diagnosis of ACE-I AE. The limited number of patients treated before ICU admission emphasizes the need for early administration of the appropriate therapy.

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**Conflicts of interest**

Olivier Fain, Laurence Bouillet, Ludovic Martin, Bernard Floccard, Isabelle Boccon-Gibod are the board members of Shire, CSL Berhing, and Viropharma. For the remaining authors there are no conflicts of interest.

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