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Angioedema Due to ACE Inhibitors

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Abbreviations *AE* Angioedema · *AAE* Acquired angioedema · *ACE* Angiotensin-converting enzyme · *ACEI* Angiotensin-converting enzyme inhibitor · *ACEI-AAE* Acquired angioedema related to angiotensin-converting enzyme inhibitor intake · *APP* Aminopeptidase P · *ARB* Angiotensin receptor blocker · *BK* Bradykinin · *CPN* Carboxypeptidase N · *DPPIV* Dipeptidyl peptidase IV · *DRI* Direct renin inhibitors · *ICU* Intensive care unit · *NEP* Neprilysin · *RB2* Bradykinin receptor type II · *SNP* Single nucleotide polymorphism · *SP* Substance P

Opinion statement

Angiotensin-converting enzyme inhibitors (ACEIs) are widely used for treatment of hypertension, congestive heart failure, and cardiovascular and renal protection in patients with heart failure, among others. Angioedema is a rare but potentially fatal adverse event (ACEI-AAE), whose prevalence is under 0.5 % among patients taking ACEIs and is higher among African Americans and female patients. There is no biomarker that allows diagnosis of ACEI-AAE, and the diagnosis is based on clinical history and the intake of ACEIs. Differential diagnosis with other causes of edema/angioedema must be considered. Recent classifications of angioedema can be of great help in the diagnosis process. The management of ACEI-induced angioedema involves the withdrawal of the causative drug and the treatment of the acute angioedema with different off-label drugs (icatibant, plasma-derived human C1 inhibitor protein). This manuscript will review the epidemiology, pathophysiology, genetics, clinical symptoms, diagnosis, and treatment of ACEI-AAE.

Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) act as renin–angiotensin–aldosterone system (RAAS) inhibitors by blocking the angiotensin-converting enzyme (ACE) that catalyzes the transformation of angiotensin I to angiotensin II, the principal effector peptide of the RAAS. ACEIs were commercialized in the early 1980s as treatment of hypertension and congestive heart failure, and later, ACEI indications were extended for cardiovascular and renal protection in patients with heart failure and chronic kidney disease and at high risk of cardiovascular event [1••]. Therefore, ACEIs are among the most frequently prescribed drugs in the world.

The first commercialized ACEI was captopril, and several others followed later (enalapril, lisinopril, etc.). ACEIs can be classified into subgroups according to their molecular structure: sulfhydryl-containing agents (captopril, zofenopril), dicarboxylate-containing agents (enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril), and phosphonate-containing agents (fosinopril) [2].

Angioedema (AE) consists in a local subcutaneous or submucosal swelling, which resolves spontaneously in a few hours or days [3, 4]. It is the result of an increase in vascular permeability [4], which is mediated mainly by histamine or bradykinin (BK), although leukotrienes have also been involved [3]. The most frequent type of AE is caused by histamine release and includes allergic reactions and idiopathic histaminergic angioedema, which can be part of chronic spontaneous urticaria [5•].

AE is a potentially life-threatening adverse event related to different drugs [6–8]. Drug-induced angioedema can be caused by three different mechanisms [7]. The most common type of angioedema is caused by histamine release, which could be due to allergic or non-allergic reactions [7]. An increase in leukotrienes has been associated with angioedema due to aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) [6]. Finally, a less frequent drug AE form is associated with an increase in bradykinin as is mainly produced by ACEIs [9].

In a recent classification of AE without wheals by the HAWK group, angioedema due to angiotensin-converting enzyme inhibitors (ACEI-AAE) was included as an acquired type of non-histaminergic angioedema due to an increase in BK favored by inhibition of ACE, which resulted in inhibition of bradykinin catabolism and subsequent increase in BK and angioedema [10••].

Later, Giavina-Bianchi et al. suggested classifying angioedema according to endotypes [11]. This classification divides angioedema into three subtypes: (a) mast cell and basophil-driven AE, (b) AE with an increase in bradykinin, and (c) idiopathic AE [11]. This classification considers ACEI-AAE within the acquired bradykinin excess endotype and has also the advantage of including other types of AE, such as NSAID-induced or exacerbated AE, allergic AE, and drug-induced AE [11], which had not been included in the classification of angioedema without wheals proposed by Cicardi et al. [10••].

Epidemiology

The prevalence of AE among patients taking ACEIs is under 0.5 % according to an analysis of large cohorts of hypertensive patients [12–16]. A meta-analysis of clinical trials evaluating angioedema as a side effect resulted in an incidence of angioedema of 0.30 % (95 % CI 0.28–0.32) with ACEI and 0.07 % (95 % CI 0.05–0.09) with placebo [1••]. The prevalence of ACEI-AAE is higher among African Americans, with up to a threefold greater risk than Caucasians [12–14, 17–19] and in female patients [14, 20•].

ACEI-AAE has been involved in one to two thirds of the angioedema cases that attended emergency departments [14, 21].

Pathophysiology

ACE blocking during treatment with ACEIs results in a local increase in BK because of inhibition of its catabolism [22–28]. This increase in BK results in an increase in vascular permeability and angioedema through interaction with constitutively expressed bradykinin type II receptors (RB2) [26].

An increase in substance P (SP) has also been shown to cooperate in the pathogenesis of ACEI-AAE [26, 28–30]. SP, also known as neurokinin-1 (NK1), is a potent proinflammatory peptide, produced in sensory nerves, that increases vascular permeability by acting on the NK1-receptor [31••]. SP is normally catabolized by ACE [32] and neprilysin (NEP) [31••] but also by dipeptidyl peptidase IV (DPPIV) [33]. During ACE inhibition, the increase in BK favors the SP release [34], and SP catabolism is also impaired, resulting both in an increase in SP levels.

In patients with ACEI-AAE, there is no increase in cleaved high molecular weight kininogen [35], supporting that there is no increase in BK generation but a decrease in BK catabolism [10••].

BK is a very potent vasoactive peptide, whose levels are strictly controlled by several enzymes that participate in its degradation [36]. BK is rapidly metabolized by ACE, also called kininase II, and carboxypeptidase N (CPN), also known as kininase I [37•]. Other enzymes that contribute to BK degradation are aminopeptidase P (APP), neutral endopeptidase (enkephalinase or neprilysin), DPPIV, and aminopeptidase N [31••, 37•]. Bradykinin catabolism can be seen in Fig. 1.

BK (Arg1-Pro2-Pro3-Gly4-Phe5-Ser6-Pro7-Phe8-Arg9) is quickly metabolized by ACE (kininase II), which acts as a dipeptidase and removes first Phe8-Arg9 at its carboxy-terminal [38, 39] and then Ser6-Pro7 resulting in an inactive peptide, bradykinin 1–5 (Arg1-Pro2-Pro3-Gly4-Phe5) [36]. ACE acts as the main BK inactivator (around 70 %) [40], but APP, DPPIV, carboxypeptidase N/M, and neprilysin (NEP) also inactivate BK [37•]. Membrane-bound APP catabolizes BK at the N-terminus by hydrolyzing the Arg1-Pro2 bond, producing an inactive bradykinin (Pro3-Gly4-Phe5-Ser6-Pro7-Phe8-Arg9), which is additionally cleaved by DPPIV [38, 39], and it is known as the APP/DPPIV pathway. Membrane-bound APP accounts for approximately 20 % of circulating BK catabolism and 65 % of circulating des-Arg7-BK [41]. NEP, an endopeptidase, also inactivates BK by cleaving the Pro7-Phe8 bond [29].

Carboxypeptidase N (kininase I) removes "Arg9" from the bradykinin C-terminal and forms des-Arg9-bradykinin, an octapeptide [31••, 36]. The resulting des-Arg9-bradykinin cannot act on RB2, but can interact with bradykinin receptor type I (RB1) induced by inflammation (e.g., interleukin-1 and tumor necrosis factor alpha) in the vasculature and cause hypotension. des-Arg9-bradykinin is subsequently excided by ACE into inactive peptides: a tripeptide, Ser6-Pro7-Phe8, and a pentapeptide, Arg1-Pro2-Pro3-Gly4-Phe5 [36].

The involvement of bradykinin in ACEI-AAE pathophysiology is supported by the fact that impairments in bradykinin catabolism, which increase bradykinin levels, are associated with the risk of having ACEI-AAE [28, 29, 40–44]. Thus, ACEI-AAE has been associated with low APP plasma activity [41, 43–45] and decreased DPPIV activity [28, 29].

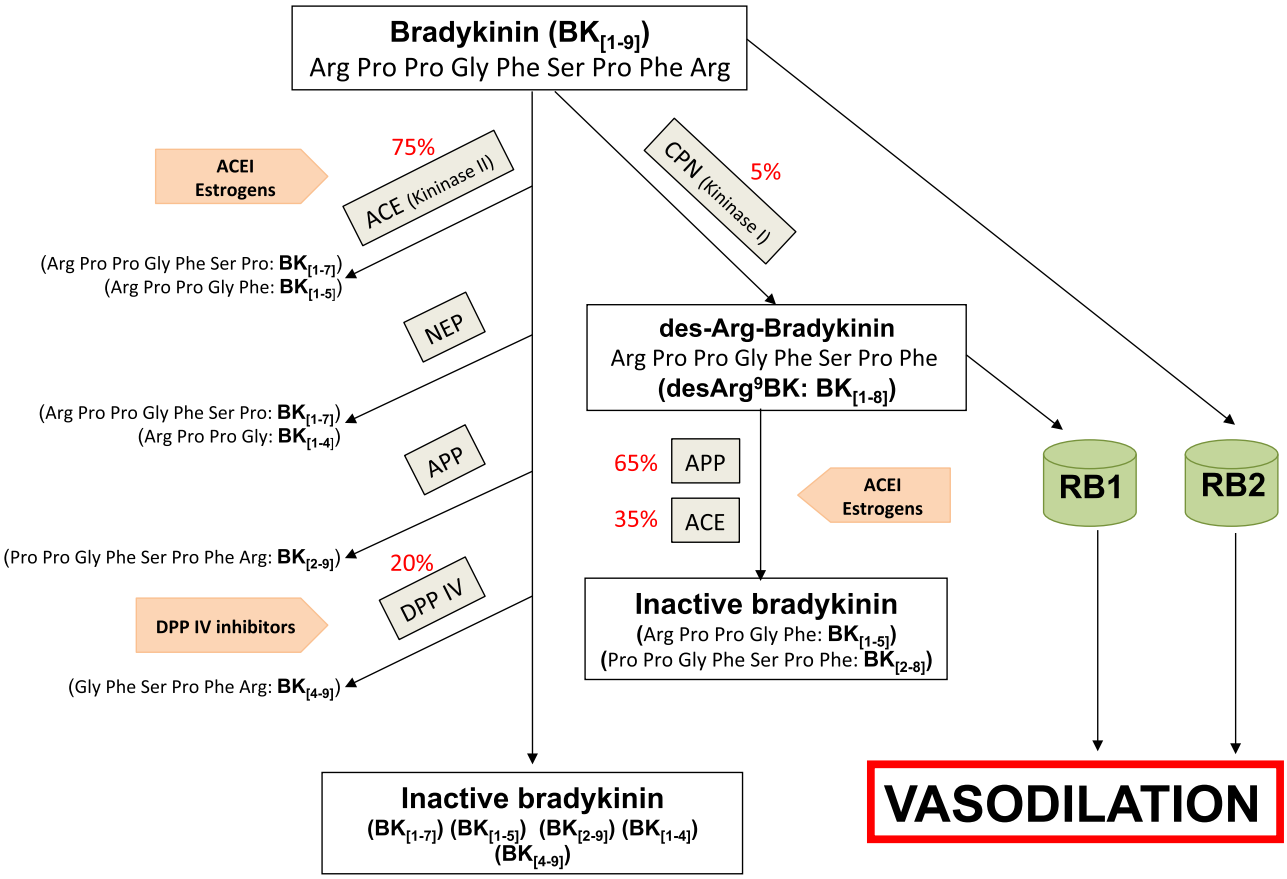

Fig. 1. Catabolism of bradykinin. *ACE* angiotensin-converting enzyme; *ACEI* angiotensin-converting enzyme inhibitor; *APP* aminopeptidase P; *BK* bradykinin; *CPN* carboxypeptidase N; *DPPIV* dipeptidyl peptidase IV; *NEP* neprilysin; *RB1* bradykinin receptor type I; *RB2* bradykinin receptor type II.

During exogenous ACE inhibition, kininase I (CPN) takes a more important role in BK catabolism with an increase in des-Arg9-BK [31••, 42, 46], and the role of EPP and APP/DPPIV in BK catabolism would also increase [42, 47, 48], with APP being mainly responsible for BK and des-Arg-BK inactivation. From a theoretical point of view, low levels of these enzymes (APP, CPN, DPPIV, EPN) could facilitate ACEI-AAE. Recently, a case report of ACEI-AAE during co-treatment with gliptins has been published in which decreased levels of three different kinin catabolizers were found [49].

Concomitant drugs and increased risk of ACEI-AAE

Gliptins (sitagliptin, vildagliptin saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, and omarigliptin) are DPPIV inhibitors.

Gliptins inhibit degradation of incretins [(glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP)] [50]. As a result, there is an increase in incretin levels, which inhibits glucagon release, stimulates insulin release from pancreatic islets in response to oral carbohydrates, and improves glucose tolerance as shown by a significant decrease in fasting blood glucose and glycated hemoglobin (HbA1c) [51]. Therefore, gliptins were marketed for the treatment of type 2 diabetes [50]. Gliptins also inhibit DPPIV and consequently impair BK catabolism. A decrease in DPPIV activity had already been described as a possible risk factor for angioedema development [52].

Vildagliptin as monotherapy was not found to increase the incidence of AE in a meta-analysis that assessed different phase III randomized clinical trials [53]. However, vildagliptin was found to increase by more than fourfold (odds ratio 4.57 [95 % confidence interval 1.57 to 13.28]) the AE incidence in patients who were concomitantly taking ACEIs [53]. This increased risk of angioedema when taking simultaneously ACEIs and a gliptin was confirmed in a study in which saxagliptin or placebo was used (0.1 vs. 0.01 %) [51].

Further studies are needed in order to improve knowledge on the true risks for angioedema when taking gliptins alone or in combination with ACEIs.

Genetics

Although ACEI-AAE is not a hereditary disease, several genetic polymorphisms have been proposed to increase the risk of having ACEI-AAE.

First, polymorphisms related to genes coding for bradykinin catabolizers have been studied. Regarding the *ACE* gene, located in chromosome 17, there is a polymorphism which consists in the deletion (D)/insertion (I) of 287 pair of bases. The polymorphism ACE-II has been associated with lower ACE plasma levels than the genotype ACE-DD and development of ACEI-AAE in African Americans but not in Caucasians [54, 55, 56•, 57••].

Membrane-bound APP is the main BK catabolizer when ACE is inhibited by ACEI intake and is coded by the *XPNPEP2* gene at the locus Xq25-26.1 [58, 59]. APP activity varies in relationship with different genetic factors. The single nucleotide polymorphism (SNP) c.-2399C>A (C-2399A) (rs3788853) in the *XPNPEP2* gene, which codifies for membrane APP, was the first polymorphism associated with a lower APP activity and a significant association to ACEI-AAE [44]. The SNP c.-2399C>A in the *XPNPEP2* gene was later confirmed to be associated with ACEI-AAE in males [odds ratio 2.17 (1.09–4.32), $p = 0.03$], but not in females [60]. Later, two other polymorphisms in the *XPNPEP2* gene (c.-1612G>T and c.-393G>C) were also associated to a decreased APP activity and ACEI-AAE [40]. APP plasma activity is lower in patients with the haplotype ATG of these three polymorphisms, and this haplotype is more prevalent in patients with ACEI-AAE and is a better predictor than polymorphism c.-2399C>A itself [40]. However, these data contrast with the results in a whole genome-wide association study (GWAS), in which no association was found between the polymorphism c.-2399C>A and the risk of ACEI-AAE [57••].

In a study of candidate genes, the presence of allele G of the polymorphism rs989692 in the intron 1 of the *MME* gene which codifies neprilysin (also known as membranous metaloendopeptidase (MME)), another enzyme which degrades BK and SP, was significantly associated with ACEI-AAE in African

Americans [57••]. The importance of this risk factor is supported by the fact that omapatrilat (a dual ACE plus neprilysin inhibitor) produced a higher number of severe angioedema than ACEIs in clinical trials [61, 62].

Several groups have studied polymorphisms in genes coding for BK receptors and its relationship with ACEI-AAE. A variant in the *BDKRB2* gene coding for RB2 (presence or absence of repetition of nine pairs of bases in exon 1) affects RB2 transcription. The presence of allele -9 of the −9/+9 polymorphism in the *BDKRB2* gene coding for RB2 has been found to be associated with higher risk for ACEI-AAE [56•]. However, no relationship between the presence of other polymorphisms in genes coding for RB2 or RB1 and risk of ACEI-AAE has been found [55, 56•, 57••], and thus, neither the polymorphisms 2/3 c-C181T [55], c-58T [56•], and c-917G>C [57••] in the gene coding for RB1, nor the polymorphism c-192C>T in the gene coding for RB2 [57••] have been found to be associated with ACEI-AAE.

A significant association has been found between the presence of the polymorphism (rs2786098) in the *CRB1* gene, which codes for a Crumbs homologous protein in Drosophila, and ACEI-AAE in African Americans, but its meaning in the pathophysiology of angioedema is unknown [57••].

Besides, Pare et al. in a GWAS study found a decreased risk of ACEI-AAE in subjects that had the allele T of the polymorphism rs500766 in the *PRKCQ* gene which codes the protein Kinase θ (PRKθ) and is important for T cell activation [57••]. In this study, the presence of allele G of the polymorphism rs2724635 in the *ETV6* gene (variant ETV of gene 6, also known as TEL), which codes a family of ETS transcript factors, was associated with an increase in ACEI-AAE. These two genes are involved in the regulation of immune system, and thus, it has been suggested that ACEI-AAE could be associated to environmental or genetic factors that decrease TH1/TH2 cell ratio.

Finally, a study combining GWAS technology and candidate gene polymorphisms (genes coding for BK- and SP-degrading enzymes: CPN, EPN, APP, DPPIV; RB1; RB2; NK1 receptor) concluded that no isolated gene could have an important effect in the development of this pathology [57••].

Although data about genetic predictors for ACEI-AAE are limited, it seems that there is no single factor with an important effect on ACEI-AAE development and probably a combination of predisposing factors would be necessary for its development. More research in this direction is needed in order to have more information that allows including angioedema-related genes into prediction algorithms to choose the best antihypertensive drug for every patient.

Clinical presentation

The typical presentation of ACEI-induced angioedema is a slow-onset subcutaneous swelling associated with neither itching nor urticaria. Involvement of the orofacial region is the most common localization. Swelling of the tongue is the most frequent presentation, affecting 39–89 % of the patients, followed by angioedema of the lips in 26–60 % [63, 64, 65•, 66••, 67, 68, 69•]. Larynx is affected in 23.3–48 % depending on the series consulted [65•, 66•, 67, 68, 69•]. The average age at presentation of symptoms is 60–65 years, after receiving ACEIs in many cases for more than 1 year [64, 65•, 68, 69•, 70]. Table 1 summarizes clinical characteristics of patients with ACEI-AAE of recently published series.

Table 1. Characteristics of patients with ACEI-AE

Reference	Number	Age (years)	Male	Localization of attacks	Time from onset ACEI to AE episode	Admission	Admission to ICU	Airway intervention
Gang et al. [63]	100	59	53 %	89 % tongue 12 % breath difficulties	–	66 %	–	2 %
Gandhi et al. [64]	60	72	51.7 %	73 % tongue 42 % lips 21.7 % voice changes 20 % diff. swallowing	1/3 more than 24 months	46.7 %	20 %	3.3 %
Javaud et al. [65•]	62	63	56 %	55 % upper lip 44 % tongue 42 % cheeks 40 % lower lip 24 % larynx	Median 12 months (range 1–49)	42 %	7 %	1.6 %
Bova et al. [67]	13	74	77 %	77 % tongue 38 % lips 23 % larynx 23 % cheeks	–	0 %	0 %	0 %
Chan and Soliman [68]	88	59.3	47.5 %	60.2 % lips 39.7 % tongue 29.5 % larynx 17 % soft palate/uvula 12.5 % face 6.8 % floor of mouth	50.7 % more than 12 months	61.3 %	52 %	31.8 %
Kieu et al. [72•]	311	59	45.3 %	54.5 % upper lip 44.5 % lower lip 32 % tongue 13.5 % larynx	–	96 %	47 %	17 %
Faisant et al. [69•]	112	65	61.6 %	48.2 % tongue 23.2 % larynx	Median 720 days (range: 1–5400) 30 % in the first 3 months	40.2 %	17.8 %	–

It is worth noting that admission to the intensive care unit (ICU) and the necessity of airway intervention are frequent in some of the published series [68, 72•]. Some studies have evaluated potential predictors for admission or the need of any kind of ventilatory assistance in these patients. In the French study by Javaud et al. [65•], the rate of admission was higher in patients presenting with laryngeal attack (OR 6.2) and in those with progressive swelling (OR 5.9). Some recent studies [63, 68, 70] have shown that patients with AE involving tongue, larynx, or floor of the mouth are more prone to need airway intervention and ICU admission, whereas lip involvement was a negative predictor. The symptoms that predicted larynx affection were voice change and dyspnea. Kieu et al. [72•] evaluated airway status by flexible laryngoscopy in ACEI-AAE patients revealing that those reporting dysphagia (OR 4.8, 2.5–8.9, $p < 0.001$), dysphonia (OR 5.4, 2.9–10.2, $p < 0.001$), globus sensation (OR 2.7, 1.4–5.1, $p < 0.001$), drooling (OR 9.2, 4.1–20.5, $p < 0.001$), and respiratory distress (OR 3.2, 4.2–16.0, $p < 0.001$) were more likely to require airway intervention. True vocal cords (OR 33.5, 3.9–285, $p < 0.001$), soft palate (OR 12.3, 5.1–30, $p < 0.001$), tongue (OR 11.1, 5.5–22.4, $p < 0.001$), aryepiglottic folds (OR 8.5, 3.8–18.7, $p < 0.001$), and vallecula (OR 9.9, 3.6–26.9, $p < 0.001$) were predictors for ventilatory support, whereas isolated involvement of the face (OR 0.4, 0.2–0.9, $p < 0.05$), upper lip (OR 0.3, 0.1–0.5, $p < 0.001$), and lower lip (OR 0.4, 0.2–0.9, $p < 0.01$) was at very low risk.

A recent retrospective study evaluated differences in clinical presentation between ACEI-AAE and hereditary angioedema (HAE) [71•]. This study has shown that ACEI-AAE patients are significantly older than HAE patients (median age 67 vs. 39 years, $p < 0.001$) and that there was a significant preponderance of localization in the face in ACEI-AAE patients (85 % of the attacks vs. 14 %), tongue (50 vs. 3 %), lips (67 vs. 8 %), cheeks (40 vs. 7 %), and larynx (44 % vs. 5 %). Conversely, these authors did not find any abdominal AE in ACEI-AAE patients, whereas in HAE patients 49 % of the attacks affected the gastrointestinal tract. Although the vast majority of AE attacks in ACEI-AAE patients affect the orofacial region, in contrast with the results of the previously mentioned study, there have been some reports on abdominal involvement in ACEI-AAE patients [73, 74]. These cases were diagnosed by CT scan, or other image technique, revealing wall thickening and fluid in the peritoneal cavity. All the patients presented abdominal pain, where other causes had been excluded and relapsed after withdrawal of the culprit drug.

Diagnosis

Diagnosis of ACEI-AAE is clinical, as there are no biological markers that can help us in the diagnosis. A diagnosis of ACEI-AAE should be considered in the case of patients taking ACEI at the moment of presentation or within the previous 6 months [75]. Nevertheless, we have to keep in mind that histamine-mediated AE is more frequent (even in patients taking ACEIs), so clinical presentation has to be considered before making diagnosis. Exposure to potential allergens; symptoms evoquing anaphylaxis, urticaria, and pruritus; and the efficacy of antihistamines, corticoisteroids, or adrenaline should drive the suspicion toward histamine-mediated AE, rather than ACEI-AAE. Clinical presentation involving the face, tongue, or ENT area is highly suspected of being

ACEI related. Some epidemiological factors could raise the suspicion, as African Americans, female gender, being more than 65 years old, and smoking habit.

Despite that there is no biological marker for ACEI-AAE diagnosis, patients are deemed to specialized consultation in order to rule out other possible causes of angioedema by dosing C1-inhibitor concentration and activity, in C1q and anti-C1-inhibitor antibodies.

Management of ACEI-AAE

The mainstay of treatment of drug-induced BK-AE is to avoid further intake of the causative drug. The use of another ACEI is contraindicated as this is a class adverse event and not a hypersensitivity reaction. Angiotensin receptor blockers (ARBs) are a good alternative for those patients needing the blockade of the renin–angiotensin cascade (e.g., cardiac protection) and can be used as the incidence of angioedema has been reported to be low, similar to placebo [1••, 76••], which is consistent with its mechanism of action. ARBs do not have an impact on BK degradation, as they only block angiotensin II receptors. Switching ACEIs to ARBs in these patients is safe [77], but close monitoring is needed. Despite withdrawing the drug, up to 30 % of patients can have a new event of AE, even after 6 months [69•], so patients should be warned about this issue. Nevertheless, 82 % of the patients show a complete remission or a reduction in the frequency of attacks of at least 75 % [78•].

The first priority after arrival to the emergency room (ER) is assessment and airway protection. There is some controversy on the use of fiberoptic laryngoscopy to evaluate the airway, as it may potentially aggravate the episode, and thus some authors advise against its use [75]. Nevertheless, this procedure allows assessment of the airway in cases where the patient has signs or symptoms of laryngeal edema such as voice changes, dysphonia, dysphagia, stridor, drooling, or respiratory distress, helping to ensure a rapid airway protection if necessary [68, 79•]. Patients presenting with symptoms identified as risk factors (e.g., tongue involvement, angioedema affecting larynx, or the lack of improvement during ER course) should be considered for admission. Patients with laryngeal AE should be immediately intubated and admitted to the ICU. Patients with edema of the floor of the mouth should be considered for intubation too. Patients with pharynx or tongue involvement or those not improving while on ER should be admitted to a monitored bed. AE limited to face and lips may be observed and, provided no progression, discharged home [79•].

To date, there is no specific treatment approved for ACEI-AAE. As BK is involved in the pathophysiology of this type of AE, symptomatic treatment with antihistamines, corticosteroids, and epinephrine may not be effective. The specific treatment for ACEI-AAE should be headed toward BK. Given that the mediator of this condition is the same as in HAE-C1-INH, therapeutic strategies with agents currently licensed for this disease have also been tried in ACEI-AAE.

Fresh frozen plasma (FFP) has been used in some case reports [80, 81]. The rationale for using FFP in the treatment of ACEI-AAE is that it provides kininase II (ACE) that degrades excessive BK. In these cases, FFP has successfully been used after not obtaining relief from conventional therapy. Nevertheless, there is also a case report of a patient treated with FFP in addition to conventional therapy that did not relapse [82].

C1-inhibitor (C1-INH) concentrate is used in HAE as it replaces the malfunctioning or missing protein helping to decrease BK production. Some case series have been published using C1-INH concentrate in patients who had been treated with conventional therapies and had progression of the edema; after the infusion of C1-INH concentrate, the episode resolved [83, 84]. A retrospective review of a German case series [85] treated with C1-INH concentrate showed a faster resolution (time to complete resolution 10.1 ± 3 h) of the episodes when compared to a retrospective cohort of patients treated with conventional therapy (33.1 ± 19.4 h), so this treatment may have a potential role in the treatment of ACEI-AAE.

Ecallantide is a selective, highly potent, and reversible inhibitor of human plasma kallikrein that binds to plasma kallikrein, inhibiting the conversion of high-molecular-weight-kininogen to BK. Ecallantide will not block neither clear existing BK, but will stop further production. Results from two studies assessing the efficacy of ecallantide in ACEI-AAE have been recently published [86, 87•]. The pilot study [86] aimed to compare ecallantide versus placebo after receiving a dose of antihistamine and corticosteroid in patients with ACEI-AAE. The primary end point was achieving objectively defined ER discharge criteria within 4 h. These criteria were met in five patients (21 %) receiving placebo and in eight patients (31 %) receiving ecallantide. Although not stated in the paper, this difference was not significant ($p = 0.526$). Further results of a multicentre randomized placebo-controlled trial [87•] following the same design have been published showing that there were no statistically significant differences ($p = 0.141$) between groups, neither when analyzing a subset of patients with more severe symptoms (Ishoo III–IV) ($p = 0.146$). With these results, the addition of ecallantide to conventional therapy has failed to demonstrate benefit and is not currently recommended.

Icatibant acetate is a synthetic decapeptide, highly specific second-generation antagonist of the bradykinin B2 receptor and inhibits vasodilator effects produced by BK, currently licensed for the treatment of HAE-C1-INH acute attacks. Some case series had been reported showing the efficacy of icatibant in ACEI-AAE [67, 88–90]. The results of a phase 2 placebo-controlled trial comparing the use of a single dose of icatibant 30 mg subcutaneously versus prednisolone 500 mg and clemastine 2 mg intravenously for the treatment of ACEI-AAE have been recently published [66••]. Patients who were treated with icatibant showed a shorter median time to complete resolution (8.0 h, IQR 3.0–16.0) as compared to placebo (27.1, IQR 20.3–48.0, $p = 0.002$) and shorter time to onset of relief (2.0 h, IQR 1.0–8.1 vs. 11.7 h, IQR 8.0–18.0, $p = 0.03$), and the percentage of patients with complete resolution was also greater in the group treated with icatibant (38 %) than in the placebo group (0 %) ($p = 0.02$). Nevertheless, there are some concerns about the cost-effectiveness of this approach [91] and whether this treatment would be as effective in more severe forms of AE or in the afro-American population [92], as in the trial all the patients were white. Despite this, given that ACEI-AAE affecting the orolaryngeal region is potentially life-threatening, it seems reasonable to administer off-label this specific treatment to these patients [93].

BK-impaired catabolism has been involved in ACEI-AAE. Some polymorphisms in the genes coding for other enzymes catabolizing BK (DPPIV, APP, etc.) can worsen ACEI-AAE. New drugs blocking BK generation (ecallantide,

pdhC1INH) or RB2 (icatibant) have been used in ACEI-AAE with variable results. More studies are necessary to obtain a safe and efficacious treatment for ACEI-AAE.

Compliance with Ethical Standards

Conflict of Interest

Dr. María Pedrosa reports personal fees from Shire HGT and CSL-Behring and was a subinvestigator in clinical trials for CSL-Behring and Shire HGT, outside the submitted work. Dr. Teresa Caballero reports speaking, consulting, and funding for meeting attendance from Shire HGT, CSL-Behring, and Novartis. She also reports funding for manuscript writing from Shire HGT and CSL Behring, and she was the principal investigator in clinical trials for Shire HGT and CSL Behring.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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