



A score for the differential diagnosis of bradykinin- and histamine-induced head and neck swellings

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Abstract

Purpose Acute edema of the head and neck region may lead to life-threatening dyspnea and require quick and targeted treatment. They can be subdivided in bradykinin- and histamine-mediated swellings, which require treatment with different classes of pharmaceuticals. Clinical pathways for differential diagnoses do not exist so far, although it is known that early treatment is decisive for faster symptom relief and reduced expression of the swellings. Aim of the study was the creation of a clinical algorithm for identification of bradykinin-mediated angioedema.

Methods 188 patients that presented to our outpatient department between 2010 and 2016 with an acute, non-inflammatory swelling of the head and neck region were included in our retrospective study. All available anamnestic and clinical parameters were obtained from patient files. Parameters showing significant differences between the two groups were included in our score. Utilization of the Youden's index allowed determination of an optimal cut-off value.

Results 76 patients could be assigned to the histamine and 112 patients to bradykinin group. The following parameters were included in our score: age, dyspnea, itching or erythema, glucocorticoid response and intake of ACEi/AT-II blockers. The cut-off value is set at three points. The proposed score yielded a sensitivity for identification of bradykinin-mediated angioedema of 96%, a specificity of 84%, a positive predictive value of 91% and a negative predictive value of 93%.

Conclusions Utilization of the proposed score allows quick and reliable assignment of patients to the correct subgroup and thereby reduces time for treatment.

Keywords ACE inhibitor · Angioedema · Bradykinin · Histamine · Urticarial · Differential diagnosis

Introduction

Acute episodes of swellings or angioedema in the head and neck region—in particular pharyngeal or laryngeal attacks—may lead to life-threatening events and require immediate measures. The morbidity of 15–30% due to asphyxiation following laryngeal attacks emphasizes the importance of rapid diagnosis and treatment [1, 2].

Generally, head and neck edema can be divided into inflammatory and non-inflammatory forms. Approximately 80% of all acute edema are of inflammatory origin and caused by local inflammatory diseases. These are easily diagnosed by detailed clinical examination, rapid blood tests such as C-reactive protein and complete blood count,

and if necessary through appropriate medical imaging (e.g. ultrasound, computer tomography) [3].

Non-inflammatory edema can be divided into bradykinin- and histamine-mediated forms, which are difficult to distinguish from one another due to their similar clinical appearance. Additionally, there are no quick blood tests which allow clinicians to differentiate them.

Bradykinin-mediated angioedema is caused either by a decreased degradation or an increased synthesis of bradykinin. Binding of bradykinin to its two receptors BR1 and BR2 leads to an increase in vascular permeability and vasodilatation [4]. The C1 inhibitor plays a key role in the production of bradykinin; it inhibits factor XII and prekalikrein whose activation would otherwise lead to generation of plasma kallikrein, proteolysis of high-molecular weight kininogen and subsequent release of bradykinin [5, 6].

Bradykinin-mediated angioedema can be further differentiated into hereditary, acquired, and renin–angiotensin receptor blocker-induced angioedema.

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The largest group among the bradykinin-mediated swellings is the Renin–Angiotensin–Aldosterone System (RAAS) blocker-induced angioedema (RAE). It can be caused by angiotensin converting enzyme inhibitors (ACEi) and angiotensin-II receptor blockers (ARBs).

ACE inhibitor-induced angioedema is a well-known adverse drug reaction with a described incidence between 0.1 and 0.7%. Reduced metabolism of bradykinin via ACE has been discussed as the underlying pathomechanism of this side effect. So, decreased degradation of bradykinin via ACE inhibitors and the subsequent elevation of bradykinin levels cause angioedema via the B2 receptor [7–9].

The reported incidence of angioedema due to therapy with ARBs is 0.1–0.4%. The inhibition of Angiotensin II receptor leads to a compensatory increase in angiotensin II levels as well as increased binding to the Angiotensin-II receptor, subsequently elevating bradykinin concentrations [9–11].

Hereditary angioedema is associated with a C1 inhibitor deficiency (hereditary angioedema type I–II) and is an autosomal dominant disease. The lack or dysfunction of C1 inhibitor leads to uncontrolled formation of bradykinin by missing inhibition of the above-mentioned kallikrein–kinin system [5]. The third type of hereditary angioedema (or hereditary angioedema with normal C1 inhibitor) is characterized by a normal C1 inhibitor activity and concentration, and caused by a mutation in the gene coding for the coagulation factor XII. This condition affects mainly women. The clinical appearance and therapy is similar to the other hereditary forms [12].

In acquired angioedema consumption of C1 inhibitor via autoantibodies leads to swellings. Auto antibody formation is closely associated with lymphoproliferative diseases [13].

Bradykinin-mediated angioedema responds poorly to the treatment with glucocorticoids and antihistamines [3, 7, 9] and should be treated with either intravenous application of the missing C1 inhibitor, subcutaneous application of a bradykinin-B2 receptor antagonist or kallikrein inhibitors. In case of ACEi- or ARBs-induced angioedema, the intake of those medications should be immediately stopped [14–16].

Histamine-induced angioedema results from a release of histamine stimulated by degranulation of mast cells or basophils, often triggered by immunoglobulin E (IgE) against auto-antigens, leading to an increase in vascular permeability. Approximately 0.1–0.8% of the population is affected by chronic urticaria. The swellings involve the superficial skin layers including lips and tongue. Response to treatment with glucocorticosteroid and H1 antihistamines is excellent [17–19].

While glucocorticoids and H1 antihistamines are cheap and usually available anytime and anywhere, C1-INH concentrate and B2 receptor blockers are expensive and, therefore, usually available only in tertiary care hospitals [20].

Furthermore, it is well known that early treatment of attacks decreases the time to remission and severity of angioedema. This leads to a reduction in the rate of tracheal intubation, tracheotomy and intensive care management. The faster the patient can be treated with the appropriate medication the sooner the symptoms stabilize [21, 22]. It is, therefore, of paramount importance to distinguish early between histamine- and bradykinin-mediated swellings to ensure effective treatment.

Currently, there are no clinical parameters to ensure a reliable differentiation between bradykinin- and histamine-induced angioedema [8, 23]. Although it is possible to identify hereditary or acquired angioedema by different laboratory markers (levels of C1 inhibitor activity and concentration, complement factors C3, C4 and C1q, genetic analysis of possible mutations of the C1 inhibitor gene), those tests are time consuming and results cannot be expected in the acute setting. Laboratory markers for the diagnosis of RAE are still not available [21].

The aim of the current study was to establish a clinical algorithm to distinguish between the two entities.

Materials and methods

Patients

188 patients (96 women and 92 men) aged from 19 to 96 years presenting between 2010 and 2016 to our ENT outpatient department with an acute angioedema attack were included in our retrospective analysis.

All obtained data were derived from our outpatient department's files and patient's discharge letters.

After detailed medical history had been obtained, all patients underwent a full ear–nose–throat mirror examination (examination of ears, nose, naso-/oro-/hypopharynx, larynx) and laboratory sampling (including ACE, C3, C4, cholinesterase, CRP, total protein, fT3, fT4, TSH, gamma GT, GOT, GPT, BUN, creatinine, potassium, sodium, aPTT, INR, fibrinogen, C1 inhibitor levels, factor XII, IgE, full blood count and C1q) was performed.

The following individual parameters were recorded and compared: age, sex, dyspnea or globus sensation, itching or erythema, localisation of the swelling (e.g. the larynx), improvement or lack thereof after treatment with glucocorticoids or antihistamines, intake of ACE inhibitors or ARBs and potential trigger factors (including patient's medication history, history of physical or mental stress, puberty, menopause, surgical interventions). Included in this analysis are only those patients for whom the above-mentioned clinical and laboratory parameters could be obtained.

Patients were invited for a follow-up visit 3 months after the initial attacks to determine if any relapse had occurred

and were then attributed to their respective subgroups: acute urticaria, chronic urticaria, allergic reaction, hereditary angioedema, acquired angioedema and ACEi- or ARB-induced angioedema.

Patients were attributed to the respective diagnostic subgroups using the diagnostic algorithm proposed in the current WAO guideline for the management of urticaria [24].

Urticaria was defined as the occurrence of recurring spontaneous wheals, angioedema, or both. Medical history was focused on the determination of possible causative factors as recommended in the WAO guideline [24]. If wheals or angioedema occurred for less than 6 weeks, patients were attributed to the subgroup acute urticaria (AU), if they lasted 6 weeks or longer they were attributed to the subgroup chronic urticaria (CU).

The diagnosis of idiopathic histaminergic angioedema (IH-AAE) was classified when patients presented with angioedema without wheals, family history had been negative and known causes of angioedema had been excluded and anti-histamine treatment had proved effective in stopping angioedema recurrence in accordance with current guidelines [25].

In patients with hereditary or acquired angioedema, we determined typical anomalies in the laboratory results (C1 inhibitor activity < 50%, elevated factor XII levels > 120%), mutations in the FXII gene, reduced (C4 < 10 or C1q < 50 mg/dl) with angioedema of skin, gastrointestinal tract or upper airways without wheals, erythema or itching.

Patients treated with ACEi or ARBs, presenting with angioedema of the head and neck without urticaria, wheals, history of urticarial angioedema or angioedema in any region of the body apart from the head and neck area were defined as RAE. Furthermore, patients must remain relapse free after stopping the intake of ACEi/ARB. This was ensured via follow-up calls after 6 months.

Patients were attributed to the subgroup idiopathic non-histaminergic angioedema (InH-AAE) when they presented with angioedema without wheals, family history had been negative and known causes of angioedema had been excluded and anti-histamine treatment had proved ineffective in accordance with current guidelines [25].

Statistical analysis and score development

Graph Pad Prism 6 (San Diego, CA) was used for statistical analysis. Differences between the groups were analyzed using bi-tailed Fisher exact test for categorical, and the unpaired student's *t* test for continuous variables. Receiver operating characteristic analysis and subsequent Youden test were applied to assess optimal cut-off values for continuous variables.

Parameters showing significant differences between the groups ($p < 0.05$) were included in our score.

Results

76 patients could be assigned to the histamine while 112 patients could be assigned to the bradykinin group.

The histamine group consisted of 35 male and 41 female patients with an average age of 60.7 years and a median age of 52 years. 42% ($n = 32$) reported globus sensation or dyspnea, 53% ($n = 40$) suffered from pruritus or erythema. 100% of patients treated with glucocorticoids ($n = 76$) had an improvement of symptoms, whilst 92% of patients treated with H1 antihistamines improved symptomatically ($n = 70$). The swellings were located as follows: 32.9% ($n = 25$) tongue edema, 30.3% ($n = 23$) lip swelling, 26.4% ($n = 20$) facial swellings, 10.5% ($n = 8$) angioedema of extremities, 9.2% ($n = 7$) uvula edema, 3.9% ($n = 3$) edema of the eyelids, 2.6% ($n = 2$) hypopharyngeal and 2.6% ($n = 2$) laryngeal edema.

30.2% of the patients in the histamine group suffered from chronic spontaneous urticaria (CSU), 39.5% from acute spontaneous urticaria (ASU), 9.2% presented with chronic inducible urticaria and the remaining 21.1% presented with idiopathic histaminergic edema (IH-AAE).

57 male and 55 female patients (average age 67.1 years, median age 68 years) could be assigned to the bradykinin group. 63.4% ($n = 71$) of the patients reported globus sensation or dyspnea, 0.9% ($n = 1$) itching or erythema, 10.6% ($n = 12$) improvement of symptoms after treatment with glucocorticoids and 1.4% ($n = 2$) after treatment with antihistamines. In this group, the angioedemas were located as follows: 17% ($n = 19$) facial swellings, 1.8% ($n = 2$) edema of the eyelids, 24.10% ($n = 27$) lip swelling, 4.5% uvula edema, 42.3% ($n = 52$) tongue swellings, 2.7% ($n = 3$) hypopharyngeal and 17% ($n = 19$) laryngeal edema, 3.6% ($n = 4$) edema of the extremities, 2.6% ($n = 3$) abdominal and 0.9% ($n = 1$) genital attacks.

Of these 112 patients, 75.9% ($n = 85$) were diagnosed with ACE inhibitor-induced and 8.9% ($n = 10$) with AT-II blocker-induced angioedema, 13.4% ($n = 15$) presented with an acute HAE attack and 1.8% ($n = 2$) were diagnosed with acquired ($n = 1$) or idiopathic ($n = 1$) angioedema. Patients suffering from Idiopathic edema were diagnosed by exclusion (no C1 inhibitor deficiency or other abnormalities in the complement system, symptoms matching those of hereditary angioedema, no association to intake of ACEi or ARBs) and responded excellent to therapy with bradykinin receptor blockers or C1 inhibitor concentrate.

The detailed patient's data are summarized in Table 1.

To identify the significant parameters to differentiate between histamine- and bradykinin-mediated angioedema, we calculated the *p* values of each item. Significant differences could be shown for patient's age, the presence of dyspnea, of itching or erythema, the symptomatic response

Table 1 Overview of the surveyed patient's data

	Histamine induced		Bradykinin induced		<i>p</i> value
<i>n</i>	76		112		
Age (years)					<0.0001
Average	60.47		67.13		
Median	52.5		68		
Sex	m:w = 1:1.17		m:w = 1.04:1		0.5539
Diagnosis	CSU	30.2%	RAE		
	ASU	39.5%	ACE inhibitor induced	75.9%	
	Chronic inducible urticaria	9.2%	AT II antagonist induced	8.9%	
	IH-AAE	21.1%	HAE		
			Type I	9.8%	
			Type II	0.9	
			Type III	2.7%	
			AAE	0.9%	
			InH-AAE	0.9%	
Erythema or itching	52.6%		0.9%		<0.0001
Dyspnoea or globus sensation	42.1%		63.4%		0.0047
Localisation	Face	26.4%	Face	17.0%	0.1436
	Eyelids	3.9%	Eyelids	1.8%	0.3953
	Lips	30.3%	Lips	24.1%	0.4014
	Tongue	32.9%	Tongue	42.3%	0.0712
	Hypopharynx	2.6%	Hypopharynx	2.7%	1
	Larynx	2.6%	Larynx	17.0%	0.0018
	Extremities	10.5%	Extremities	3.6%	0.0705
			Abdomen	2.6%	
Improvement	Glucocorticoids	100%	Glucocorticoids	10.6%	<0.0001
	Antihistamines	92.1%	Antihistamines	1.4%	<0.0001

to glucocorticoids, as well as the medicinal intake of ACEi or ARBs.

To develop a scoring system, we awarded each met parameter with one point and calculated the sensitivity and specificity for each cut-off value by analyzing these data using the ROC curve (*p* value < 0.0001, area under the curve 0.9777; compare Table 2). By counting a positive response to glucocorticoids doubly, we were able to notably increase the score's specificity and significance. The developed score allowed a maximum of 7 points (compare Fig. 1). Subsequent Youden test showed optimum cut-off for a score of ≥ 3 (Fig. 2).

For easy memorization and good applicability in clinical daily practice, we created the acronym "DAMSEL" (dyspnea, age, medication, steroids, erythema and laryngeal swelling).

Discussion

Acute edema of the head and neck region are potential life-threatening events that can occur in every emergency department. The differentiation of histamine- and

bradykinin-mediated acute swellings is of utmost importance and presents a diagnostic challenge in clinical practice. So far, only clinical pathways for general emergency treatment of acute head and neck swellings exist. Differentiation between histamine- and bradykinin-mediated edema does not play a role in these pathways, although this distinction is vital for the choice of the right treatment [26–29].

This differentiation becomes even more important due to the fact that bradykinin-mediated edema is increasing in incidence concurrent with the increasing number of patients being treated with ACEi and ARBs. This bradykinin-induced edema is clinically highly relevant since they frequently occur in the upper airway region and, therefore, may lead to life-threatening airway obstruction. Approximately one-third of all acute attacks of head and neck swellings are ACEi-induced edemas [30]. Previous studies have shown that early detection and therapy of bradykinin-mediated edemas decrease mortality and morbidity, and may prevent the necessity of intensive care or intubation [21]. Fast diagnosis and treatment with Bradykinin-B2 receptor blockers or C1 inhibitor concentrate are of utmost importance to prevent unnecessary hospitalization and airway interventions [11].

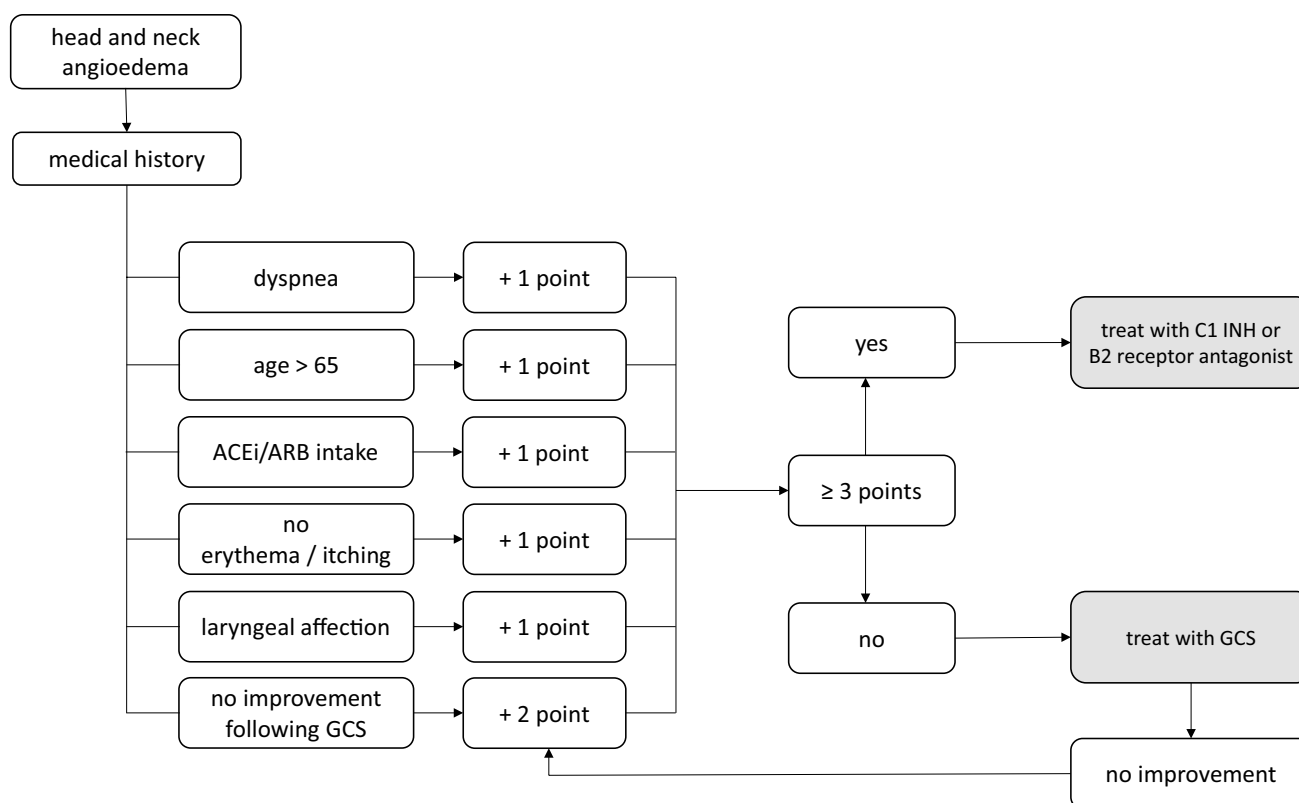


Fig. 1 Graphical flowchart of the DAMSEL protocol

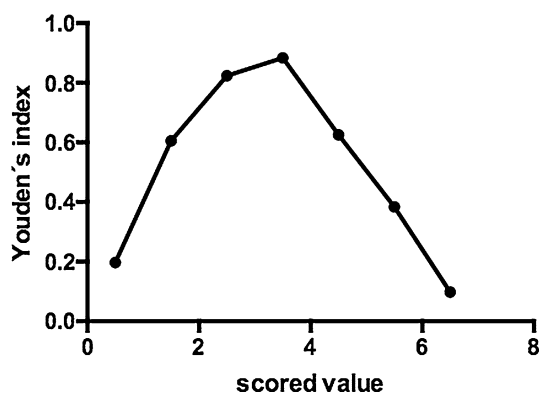


Fig. 2 Youden's index for each calculated score point

Table 2 Sensitivity, specificity, positive predictive (PPV) and negative predictive value (NPV) for the respective scoring results

Score	Sensitivity	Specificity	PPV	NPV
≥ 1	1	0.07792	0.88	1
≥ 2	1	0.4605	0.14	1
≥ 3	0.955	0.8442	0.91	0.93
≥ 4	0.8559	0.974	1	0.85
≥ 5	0.4775	1	1	0.64
≥ 6	0.03604	1	1	0.52

Measurement of bradykinin plasma levels is not viable in the clinical setting due to its short plasma half-life of about 7 s. Other laboratory markers of bradykinin activity are currently not available in the routine clinical setting [30]. Diagnosis has to, therefore, be purely based on clinical parameters. The aim of this study was to develop a simple and quickly applicable score to clearly differentiate histamine- and bradykinin-mediated angioedema in the clinical setting.

With a lifetime prevalence of approximately 20% [24], acute attacks of urticaria are way more frequent than hereditary angioedema attacks (disease prevalence of 1/10,000 to 1/100,000, mean attack frequency 3.6 to 18 attacks per year [31]), or ACEi-induced (attack incidence 0.3%) or ARB-induced (attack incidence 0.11%) angioedema [25]. Nevertheless, in our selected patient collective the group of bradykinin-mediated angioedema was predominant. This is most likely due to the fact that RAE solely affects the upper airways and the head and neck area, and may, therefore, be overrepresented in our otorhinolaryngologic collective.

Significant differences between the two subgroups could be shown for the items such as dyspnea or globus sensation, patient age greater than 65 years, intake of ACEi or ARBs, improvement of symptoms after treatment with glucocorticoids, presence of erythema or itching and the

Table 3 Comparison of the inclusion criteria of several trials concerning ACEi-induced angioedema

	DAMSEL	A randomized trial of Icatibant in ACE inhibitor-induced angioedema [7]	Recurrent angioedema; occurrence, features, and concomitant diseases in an Italian single-center study [33]	Angioedema related to angiotensin converting enzyme inhibitors [30]	Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema [34]
Age	Y	Y	N	N	Y
Dyspnea/globus sensation	Y	N	N	N	N
ACEI/ARBs	Y	Y	Y	Y	Y
Steroids	Y	N	N	Y	N
Erythema/itching	Y	Y	Y	Y	Y
Laryngeal attack	Y	Y	N	N	N

affliction of the larynx. While acute attacks of chronic urticaria mostly involve dermis, subcutis or proximal mucous membranes [32] including lip or eyelid, bradykinin-mediated angioedema are known to affect the submucosal tissue and commonly are located in the upper airway region explaining a higher frequency of dyspnea or sensation in this patient group [21]. The observed differences in patient age are most likely due to the fact that 76% of the bradykinin-induced swelling was due to ACEi or ARBs being used as a treatment for diverse cardiovascular conditions. Incidence of those diseases characteristically increases with age [33].

Lack of symptom improvement of bradykinin-induced angioedema after treatment with glucocorticoids or antihistamines is widely recognized and is due to the missing involvement of histamine and glucocorticosteroid receptors in the pathophysiology of bradykinin-induced edema. Erythema and itching are classic symptoms mediated via H1 receptors and practically never occur in bradykinin-mediated swellings [32, 34].

Several randomized controlled trials regarding diagnosis and therapy of ACEi-induced angioedema established different inclusion criteria (compare Table 3). As a result, the conclusions derived from these studies differ accordingly [7, 33, 35–37]. One possible reason for the concluded different responses to therapy could be the accidental inclusion of patients with acute or chronic urticaria. A very important first step would be to safely exclude patients with histamine-mediated edemas to gain reliable results. Our proposed score could serve as a screening tool in further trials.

Patient history in cases of acute head and neck angioedema should include the parameters highlighted in Fig. 1. The DAMSEL score is a sum score of the parameters such as patient's age, presence of dyspnea, itching or erythema, intake of ACEi or ARBs and symptomatic response to glucocorticoids. Response to glucocorticosteroids is counted doubly. While Youden's test determined the scores optimum cut-off value at 4 points, we considered a high sensitivity at the expense of a moderate decrease in specificity more

important and consequently set the cut-off value at three points leading to a sensitivity of 95% and a specificity of 84% for bradykinin-induced swellings. This decision was made because delayed treatment with anti-bradykininergic therapy considerably reduces the efficacy of the medication and because those pharmaceuticals in general have a favorable side effect profile [38].

Conclusion

In summary, an easy-to-use diagnostic score to safely differentiate between histamine- and bradykinin-mediated angioedema could be developed in our study, which will allow to expedite treatment and potentially minimize life-threatening complications in the future. To verify the scores reliability, further prospective studies are warranted.

Compliance with ethical standards

Conflict of interest M. Lenschow, M. Bas, F. Johnson, M. Wirth and U. Strassen state no conflicts of interest regarding this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent All data were assessed from daily oto-rhino-laryngologic routine. Study data were assessed pseudonymised and published anonymised. Therefore, informed consent was not necessary (in accordance with the local institutional review board guidance).

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