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ORIGINAL RESEARCH

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Recurrent angioedema: Experience at a tertiary care urban medical center

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Abstract

Objective: To determine the demographics, presentation, management, and outcomes of patients with recurrent angioedema. To compare the findings to patients with ACE inhibitor related angioedema.

Methods: Retrospective case series with chart review of patients who presented to a tertiary-care hospital between January 2010 and December 2017 with two or more episodes of angioedema. Excluded were patients with anaphylactic reaction, medication induced angioedema, or angioedema secondary to an infectious etiology. A group of 88 patients who presented during the same time period with ACE inhibitor related angioedema was used as a control. Statistical analysis was conducted using a two-tailed Fisher exact test and a multivariate logistical regression model to determine significant associations.

Results: Ninety-one patients were identified; 61 met the selection criteria and had 217 total episodes of angioedema episodes presenting to the emergency department. Fifty percent were Caucasian or Hispanic. The average number of episodes was 3.5 (range: 2-23). The lips and tongue were the most commonly affected sites (37% and 39%). The larynx and floor of mouth were least likely to be involved (7% and 6%). Only 1 patient was found to have C1 esterase inhibitor deficiency. Twenty-eight percent of patients had asthma, allergic rhinitis, food allergies, or atopic dermatitis. Only 11% of episodes required airway intervention. No patients required airway intervention after admission.

Conclusion: Recurrent angioedema was primarily idiopathic, was less severe than ACE inhibitor angioedema, and was associated with an atopic history. There was less frequent worsening of symptoms after admission, and recurrences occurred more frequently are at the same anatomic subsite.

Level of Evidence: IV.

KEYWORDS
ACE inhibitor, angioedema, C1esterase inhibitor, recurrent angioedema

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1 | INTRODUCTION

Written descriptions of angioedema date as far back as the Old Testament. However, it was Quincke's 1882 case series of patients who presented with swelling of the lips and face that is widely recognized as the first full medical report of angioedema.[1] In 1888, Osler documented a familial condition which involved asphyxiation from laryngeal edema and coined the term, hereditary angioedema (HAE).[2] The modern definition of angioedema refers to the condition of swelling in subepithelial or submucosal tissues caused by leakage of fluid from blood vessels. While this condition can affect any part of the body, it most commonly occurs in the face and perioral region. Progression of swelling into the tongue, oropharynx or larynx can lead to difficulty breathing and ultimately airway obstruction, thus making angioedema a medical emergency.[3,4]

Angioedema is a heterogeneous condition with several etiologies which can most broadly be divided into primary and secondary angioedema based on the absence or presence of urticaria respectively. Secondary angioedema, which is synonymous with anaphylaxis, is well described. The series of events that lead to its symptomatology can be traced to the exposure of a patient to a specific sensitized allergen.[4] The significant differentiating factor between angioedema and anaphylaxis is the response to epinephrine. In contrast, primary angioedema is less well understood.

The current perception of primary angioedema dates back to the work of Osler and can be broadly categorized based on the presence or absence of an inheritance pattern. Hereditary angioedema, as its name suggests, is a familial condition that has been linked to C1 esterase inhibitor deficiency (C1-INH HAE) or Factor XII deficiency (FXII-HAE) in most cases. Acquired angioedema is a distinct entity and lacks a familial pattern. While most commonly associated with angiotensin converting enzyme inhibitors (ACE-I), it can also be from an acquired C1-INH deficiency or may be idiopathic.[3,5,6] Furthermore, histaminergic forms of angioedema can be characterized by their response to antihistamines. Patients in this category may have triggers such as environmental allergens.

While these definitions are essential in differentiating subtypes of angioedema, the acute management of patients without a distinct prior diagnosis can be challenging. Multiple lab tests have been studied to determine the best predictor of angioedema. Currently, the most commonly tested measures include C1-INH, complement C4, and complement C1q.[7] In our hospital, C1-INH, C3, and C4 are routinely obtained; values below 50% of normal are considered positive. However, these tests are neither sensitive nor specific for all subtypes of angioedema, are not rapid, and do not guide acute management, but rather are helpful for future recurrences.[7] Additional information is included in Table 1.

Our institution, a large tertiary-care urban medical center, treats a large volume of patients who present with primary angioedema, and we have previously described our experiences with ACE-I related angioedema.[8-10] However, in our clinical practice, we have come to recognize an unexpectedly large group of patients who present with recurrent episodes of angioedema, most of whom fall under the acquired idiopathic primary angioedema category. The current study focuses on the inpatient management of episodes of recurrent angioedema and compares them to patients with the more common ACE-I related angioedema.

TABLE 1 Testing considerations in recurrent angioedema

Lab test	Expected value in angioedema
C1 inhibitor functional	May correlate with disease severity
C1 inhibitor quantitative	Positive if lower than 50% of normal value
Complement C1q	Normal in hereditary, reduced in acquired C1-IN
Complement C3	Positive if lower than 50% of normal value
Complement C4	Positive if lower than 50% of normal value
CBC	Normal
ESR, CRP	Normal
D – dimer	Normal
ANA	Normal
Thyroid function	Normal

Note: The above table has a list of various lab tests to consider in the work up of recurrent angioedema. The first section of tests is angioedema specific. Certain levels can be correlative of some subtypes of angioedema.[3,4,7,12,17,20]

- C1-INH HAE type 1—low C1-INH function and quantitative protein, low C4, normal C1q
- C1-INH HAE type 2—normal C1-INH protein, low function, low C4, normal C1q
- FXII-HAE and other hereditary forms—all levels normal
- Acquired C1 INH—low C1 INH function and quantitative protein, low C4, low C1q
- ACE-I and other acquired idiopathic forms—all levels normal

The second group of tests begins a work up of other possible causes of edema such as thyroid disease, autoimmune disease, and lymphoproliferative disorders.

2 | METHODS

After institutional review board approval was obtained (protocol # 24322), a retrospective review of all patients with angioedema (ICD 9 code 995.1 and ICD 10 code T78.3) presenting to Temple University Hospital between January 2010 and December 2017 was performed. Inclusion criteria were at least 2 documented episodes of angioedema in the Emergency Department or while hospitalized. Subjects were excluded if all episodes were attributable to a cause such as anaphylaxis or ACE inhibitor use, if they were improperly coded, or if there was insufficient data in the medical chart.

Specifically, if the patient had further documented systemic symptoms and met the anaphylaxis criteria described by Sampson et al, anaphylaxis was suspected and the patient was excluded.[11] A patient's clinical improvement with epinephrine was considered diagnostic of anaphylaxis. Whereas, the presence of mucosal swelling in the head and neck region without other systemic manifestations was

diagnostic of acute angioedema. In the acute inpatient setting, patients were either diagnosed with ACE-inhibitor angioedema, or non ACE-inhibitor angioedema. If patients had a history of multiple emergency department visits, a further genetic work up and lab panel workup was recommended as an outpatient. (Table 1) Upon chart review, patients were categorized as "recurrent angioedema" if they met the above inclusion and exclusion criteria, regardless of the angioedema phenotype (histaminergic vs nonhistaminergic, hereditary vs nonhereditary, etc.).[3]

The information collected included gender, ethnicity, tobacco use, comorbid medical conditions, family history of HAE, history of atopic disease, and ACE-I use. Specific atopic conditions documented were seasonal allergies, allergic rhinitis, asthma, atopic dermatitis, and food allergies. Furthermore, clinical details for each episode of angioedema, including symptoms at presentation, anatomic sites involved, laryngoscopic findings, timing of airway intervention, treatment medications, length of stay, and disposition were collected. Laboratory test results including genetic tests for HAE, and C1-INH, C3 and C4 levels were documented.

A group of 88 patients diagnosed with ACE-I related angioedema during the same time period was used as a control. A single representative year was chosen for the control group to match the number of patients in the study group, as the incidence of ACE-I angioedema is higher.

To study differences between subsequent episodes of angioedema, episodes were separated into three groups: first episode, second episode, and third-or-greater episodes. The number of anatomic subsites involved, need for airway intervention, average length of stay, and percent discharged to home were compared for the three groups.

2.1 | Statistical analysis

Descriptive statistics were used to summarize data such as patient characteristics and angioedema episodes. Risk factors for outcomes of interest were assessed using a two-tailed Fisher exact test for univariate analysis. Additionally, a multivariate logistical regression model was used to determine significant associations. *P* values of less than .05 were considered statistically significant. To determine the impact of missing lab testing data, the recurrent angioedema group was stratified into two groups based on whether C1-INH lab testing was performed. Demographics and clinical data were compared between the two groups using Fisher Exact Test.

3 | RESULTS

3.1 | Study group

During the study period, 516 patients who presented to Temple University Hospital were diagnosed with angioedema, of which 91 had at least two episodes. Of these, 10 patients were miscoded, 11 were due to ACE inhibitors, and 9 had insufficient data recorded in the medical chart; all were excluded. This resulted in a total of 61 patients which were included in the analysis (Figure 1).

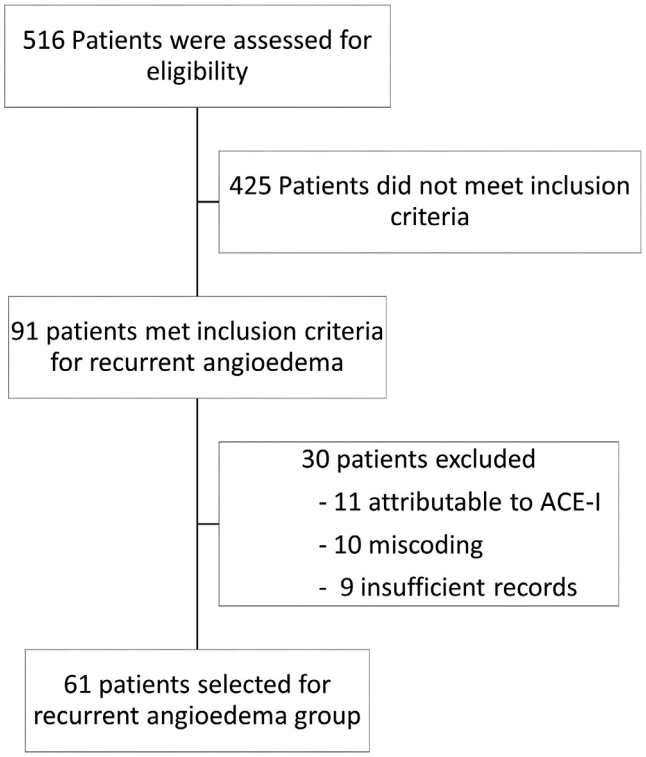

FIGURE 1 A total of 516 patients were identified who were diagnosed with angioedema during the study period. Sixty-one patients were ultimately selected for the study group after inclusion and exclusion criteria

3.2 | Control group

Eighty-eight patients who presented with ACE-I related angioedema between 1/1/2012 and December 31, 2012 were used as a control group.

3.3 | Patient characteristics

There were 38 women (62%) and 23 men. The mean age was 59.2 years (range 17-90 years). Fifty percent were African-American, 27% Caucasian, and 23% Hispanic. Fifty-four percent were either current or former smokers. The average age at presentation, male to female distribution, and smoking status were not significantly different between the recurrent and ACE-I related angioedema groups. Twenty-nine patients (48%) had C1-INH, C3, and C4 levels drawn, of which only 1 (3.4%) had a deficiency. This patient had a positive family history and was categorized as C1-INH HAE.

Significant differences in racial demographics, co-morbid medical conditions, and atopy were noted between the groups. Specifically, there was a larger proportion of patients who identified as Caucasian

TABLE 2 Patient characteristics

	Recurrent (%)[a]	ACE inhibitor (%)	*P* value when applicable
Number of patients	61	88	
Age (range)	59.2 (17–90)	59.3 (33-89)	
Sex			
Male	23 (38)	33 (37)	1
Female	38 (62)	55 (63)	1
Race			
African American	31 (50)	80 (91)	<.001
Caucasian	16 (27)	2 (2)	<.001
Hispanic	14 (23)	6 (7)	.01
Smoking status			.46
Current	22 (36)	41 (46)	
Never	28 (46)	33 (38)	
Former	11 (18)	14 (16)	
History of ACE inhibitor use	29 (45)	88 (100)	
Family history of angioedema	5 (8)	9 (10)	.78
Comorbidities			
Diabetes	17 (28)	28 (32)	.7
HTN	45 (75)	88 (100)	<.001
CAD	5 (8)	11 (13)	.59
CKD	0 (0)	9 (10)	.01
Allergic rhinitis or seasonal allergies	10 (17)	3 (3)	.007
Atopic dermatitis	2 (3)	0 (0)	.17
Asthma	14 (23)	14 (16)	.3
Food allergies	12 (20)	7 (8)	.04

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; HTN, hypertension.
[a]Percentage unless otherwise specified.

(*P* < .001) and Hispanic (*P* < .05) and a smaller proportion who identified as African American (*P* < .001) in the recurrent angioedema group. Patients in the ACE-I related group had significantly higher rates of hypertension (*P* < .001) and chronic kidney disease (*P* < .05). Rates of allergic rhinitis (*P* < .01) and food allergies (*P* < .05) were significantly higher in the recurrent angioedema group. (Table 2) These relationships remained significant on multivariate analysis.

3.4 | Individual episode characteristics

There were a total of 217 episodes of angioedema captured in the recurrent angioedema group. The mean number of episodes per patient was 3.5 (range 2-23). Thirty-two patients (52%) had only two documented episodes during the study period.

The mean time between episodes was 99 days (range 2 days to 6.8 years). The lips and tongue were the most commonly affected sites (37% and 39%), followed by the face and pharynx (13% and 11%). The larynx and floor of mouth were the least likely to be involved (7% and 6%). The mean number of subsites involved was 1.4 (range 1-3 subsites), with only 1 subsite being involved in most cases. Subsite involvement was significantly different when compared to the ACE-I related group, with the recurrent angioedema group less likely to have lip (*P* < .001) or laryngeal involvement (*P* < .001) (Figure 2).

Nearly half of the episodes of angioedema were treated in the Emergency Department and subsequently discharged (47%). Thirty-five percent of the episodes required admission to the intensive care unit (ICU) for observation. Eighteen percent were admitted to a general medical/surgical floor. Twenty-four episodes (11%) required urgent airway intervention, of which 22 were endotracheally intubated, and 2 received a surgical airway. Of note, none of the patients in the recurrent angioedema group underwent airway intervention after transfer to the hospital floor or ICU (Table 3). Tongue or pharynx involvement was predictive of airway intervention in the recurrent angioedema group (Table 4).

3.5 | Subsequent angioedema episodes

There were 156 subsequent episodes identified, defined as any episode after the first documented episode. Compared to their first episode, 65% of patients had the same anatomic subsite(s) involved on subsequent

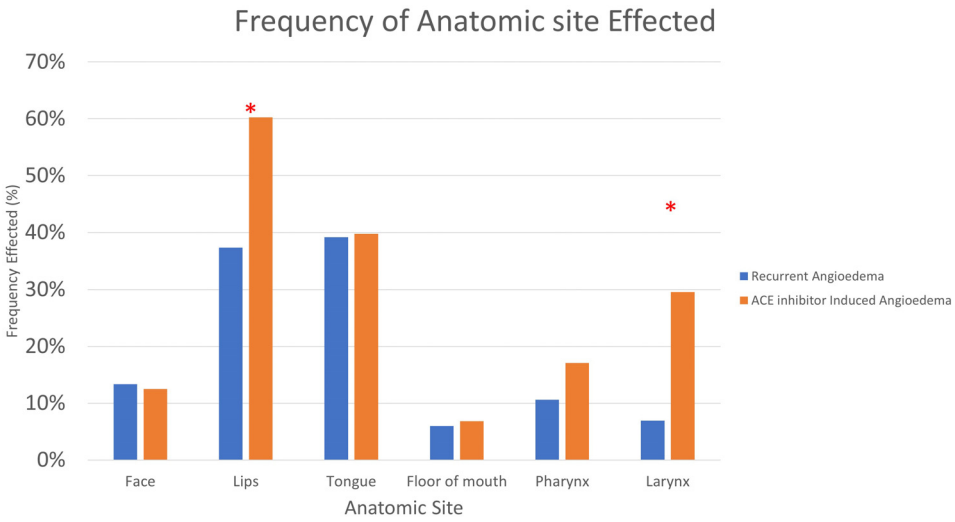

FIGURE 2 Frequency of anatomic site affected. * ACE-I related episodes were more likely to involve the lips ($P < .001$) and larynx ($P < .001$)

TABLE 3 Episode characteristics

	No. (%)[a]	ACE inhibitor (%)	*P* value when applicable
Average number of episodes per person (median, range)	3.5 (2, 2–23)	1	
Total number of episodes	217	88	
Site affected			
Face	29 (13)	11 (13)	1
Lips	81 (37)	53 (60)	<.001
Tongue	85 (39)	35 (40)	1
Floor of mouth	13 (6)	6 (7)	.8
Pharynx	23 (11)	15 (17)	.12
Larynx	15 (7)	26 (30)	<.001
Airway intervention			
Intubation	22 (10)	28 (32)	<.001
Surgical airway	2 (1)	0 (0)	1
Disposition from ED			
Discharge	102 (47)	34 (39)	.2
ICU	76 (35)	46 (52)	.006
Hospital floor	39 (18)	8 (9)	.055

Abbreviations: ED, Emergency Department; ICU, intensive care unit.
[a]Percentage unless otherwise specified.

TABLE 4 Physical exam predictors of airway intervention in recurrent angioedema

	Airway intervention	No airway intervention	*P* value if applicable
N per group	24	193	
Face	0	29	.998
Lips	4	77	.786
Tongue	16	69	***.030***
Floor of mouth	3	10	.731
Pharynx	7	16	***.011***
Larynx	4	11	.510

Bold values indicates statistical significant.

TABLE 5 Subsequent angioedema episodes

	Angioedema episodes		
	First	Second	Third or greater
Number of episodes	61	61	95
Average no. of subsites	1.47	1.35	1.40
Airway intervention	16%[a]	12%[b]	6%
Average length of stay	3	2.3	1.8
Discharged home from ED	45%	54%	42%

Abbreviations: ACE, angiotensin converting enzyme; ED, Emergency Department.
[a]First episode compared to third or greater episode is significant (P = .04). First episode compared to second episode is not significant (P = .6).
[b]Second episode compared to third or greater episode is not significant (P = .05).

episodes. In addition, there was no significant difference in the number of anatomic subsites involved between initial and subsequent episodes (1.47 vs 1.35 vs 1.47, P = .8). Fifty-two percent of subsequent episodes resulted in the same disposition and outcome (defined as the need for admission or airway intervention) as the first episode, whereas 25% resulted in a better outcome and 22% in a worse outcome. The first episode of angioedema was more likely to result in airway intervention, compared to the third-or-greater episode (16% vs 6%, P = .04). There was no difference in rates of acute airway intervention when comparing second episode of angioedema to the first or to the third-or-greater episode (12% vs 16%, P = 1.0; 12% vs 6%, P = .5) (Table 5).

All patients were treated in the acute setting with a combination of intravenous steroids and antihistamines until time of discharge. The specific regimen includes intravenous administration of dexamethasone 8 mg every 8 hours, famotidine 20 mg every 12 hours, and diphenhydramine 25 mg every 8 hours. Three patients underwent subsequent treatment trials with immunotherapy in the outpatient setting for presumed histaminergic angioedema, and the 1 patient with C1 INH HAE had success with Ecallantide therapy for subsequent episodes.

3.6 | Additional analysis

Twenty-nine patients (48%) had C1-INH, C3, and C4 levels drawn. Gender, race, smoking status, and past medical history were not significantly different between the patients who were tested and not tested (P > .05 for each). Patients selected for lab work up were had more anatomic subsites involved (P = .002), were more likely to have an atopic history (P < .0001), to be intubated (P = .0063), to have a history of ACE inhibitor use (P = .0016), and more recurrent episodes (P = .003).

4 | DISCUSSION

Determining the etiology of an individual's angioedema in the acute setting can be challenging. While a family history may be useful, it is not always telling. Although angioedema has been categorized into different well described subtypes, acute episodes are almost indistinguishable, and lab tests can take hours to days to result. In this study we attempted to identify patient factors that may correlate with outcomes.

Although C1-INH deficiency HAE is the most widely studied and characterized form of HAE, only 1 patient out of 29 who had lab workup tested positive.[12] In contrast, most published series of recurrent angioedema reported a lower percentage of patients with idiopathic angioedema.[13-15] Mansi et al reported 66% of patients as being idiopathic acquired, and 36% as having hereditary angioedema, mostly associated with C1-INH deficiency.[14] This discrepancy in C1-INH deficiency may be attributable to the fact that only 48% of our patients had relevant lab testing performed. Furthermore, our analysis of practice patterns for obtaining serum testing revealed a bias toward patients with more severe disease processes. However, while it is likely that some patients who did not have lab work up may have positive complement testing, these would have been patients with acquired C1-INH deficiency rather than a hereditary form, since most patients had a negative family history of angioedema (Table 2).

Surprisingly, other studies have shown that most patients with idiopathic acquired angioedema have more than 12 episodes annually, whereas our study group had a mean of 1.4 episodes per year.[14,16] This discordance provides further justification that presentations of recurrent angioedema in our study population are significantly different from other studies. While most large cohort studies of angioedema are from European cohorts, our series represents a large US urban medical center that sees a high percentage of African American and Hispanic patients. This implies that there may be either an environmental trigger or genetic factor that has yet to be identified that could explain the difference in angioedema presentations in Europe and the United States.[14,17]

Significant differences were noted between the recurrent angioedema and the ACE inhibitor induced angioedema groups. Patients with recurrent angioedema were more likely to be Caucasian or Hispanic, whereas ACE-I related angioedema patients were more often African-American. This finding is consistent with the current literature. Patients with recurrent angioedema also had a significantly higher rate of atopy, specifically food allergies and seasonal allergies, when compared to the ACE-I related group (Table 2). As ACE inhibitors are used in the context of hypertension and are considered renal protective, it is intuitive that the ACE-I related group was more likely to have hypertension and chronic kidney disease than the recurrent group.[18,19] It is possible that the differences in presentation of these two conditions could be attributed to a difference in genetic predisposition; however, other variables such as socioeconomic factors and environmental exposures were not assessed in this study, and could potentially be confounders. In addition, the degree of atopy was not quantified in this study, but rather a history of the diagnosis. Nonetheless, it is certainly possible that patients with a more significant atopic history have a higher likelihood to present with recurrent angioedema. Additional medications such as NSAIDs and angiotensin receptor blockers have been linked to angioedema as well. Given the

retrospective nature of this study, detailed exposure history was not available.

Additional differences were noted between the groups with regard to anatomic subsite involvement and need for airway intervention. Recurrent angioedema patients were less likely to have laryngeal involvement compared to ACE-I related angioedema patients. Consequently, recurrent angioedema patients were also less likely to be have airway interventions compared to ACE-I related angioedema patients. This is interesting and consistent with the previously described finding in the ACE-I related angioedema group that laryngeal involvement is a positive predictor for airway intervention, and worsened outcomes.[8,19-25]

The most striking finding was the difference in disease progression leading to airway intervention between the two groups. All of the airway interventions for patients with recurrent angioedema occurred in the Emergency Department. None of the recurrent angioedema episodes resulting in admission to the ICU or general medical/surgical floor unit (53% of episodes) required subsequent intubation. In contrast, 25% of the intubations in the ACE-I related angioedema patients, occurred after admission to the ICU. This finding may suggest that recurrent angioedema has a less aggressive course and is more responsive to medications than the ACE-I related subtype. Alternatively, it may be that ACE-I related angioedema has a predilection for those subsites of the airway where even minimal edema can be unforgiving.[18,26] This information can help guide clinical decision making and resource management.

Interestingly, patients with idiopathic recurrent angioedema were found to have a similar pattern of recurrence with 65% of recurrent episodes occurring at the same anatomic subsite(s) as the first episode. This was a curious new finding, as the current understanding of the pathophysiology of angioedema does not adequately explain why some episodes recur in the same region while others recur elsewhere. Finally, 77% of patients had the same or better outcome on subsequent episodes compared to their first episode. Although this may be due to the underlying pathophysiology, it is important to acknowledge potential confirmation bias in their care. It is possible that patients and providers are less concerned on subsequent occurrences either due to counseling or assurance based on previous episode. It is also possible that some patients may have started medical therapy or decreased exposure of a trigger upon subsequent presentations. Still, this data would also be useful in counseling patients and guiding care.

Many lab tests have been used to predict angioedema types, some of which are listed in Table 1. Levels of individual factors (eg, factor XII), bradykinin, angiotensin, histamine, tryptase, or leukotrienes may also be obtained. These tests were not routinely ordered for either cohort of patients. Familial mastocytosis and other similar mast cell disorders may mimic angioedema but were only considered for work up in an outpatient setting. Antihistamine trials were initiated for select patients with suspicion of histaminergic angioedema as an outpatient. The most important step in an outpatient work up is to determine if the angioedema is hereditary or an acquired deficiency, as there are effective preventative drugs for these. Furthermore, determining antihistamine response can be helpful to prevent future attacks, as immunotherapy may be considered.

Limitations of this study include its retrospective design. Patient charts were identified for review using only the ICD 9 and ICD 10 codes for angioedema, which may have missed some patients who were coded differently. The data were extracted from patient charts with significant variability in the quality of documentation including laryngoscopic findings. Furthermore, while this study was conducted at a large urban university hospital, the generalizability of this study may be limited due to differences in demographics as compared to other institutions. In addition, not all patients with recurrent angioedema had C1 INH, C3, and C4 levels checked, which may have underestimated the number of hereditary cases.

Although some may view anaphylaxis as an extreme form of histaminergic angioedema, we chose to exclude patients with anaphylactic reactions from our study group. Our distinguishing factor was a documented response to epinephrine in the chart. However, we acknowledge that patients incorrectly coded as anaphylaxis but in fact had angioedema may be missed. The decision to do so was made from a practical standpoint. While anaphylaxis may occasionally require airway intervention, recovery with epinephrine is usually significant and rapid. Consequently, we acknowledge that there may have been patients coded as anaphylaxis who could be classified as angioedema and were not included. Laryngoscopy was performed by either ED or Otolaryngology residents which may contribute to inconsistent documentation. Nonetheless, this study provides useful new information that may help guide patient care and affords a solid basis for future study of this condition.

5 | CONCLUSION

This retrospective case series demonstrates that patients with recurrent angioedema at our institution are more likely to be Caucasian or Hispanic and are more likely to have an atopic history than patients with ACE-I related angioedema. They are less likely to have lip and laryngeal involvement and are also less likely to require intubation or tracheotomy. They less frequently have worsening of their symptoms after admission, and most often recur at the same anatomic subsite. They most often have the same or better outcome on subsequent episodes. While these findings were noted in a single, large, ethnically diverse urban university hospital and need further studies to determine causality and generalizability, they provide useful insight into a less common clinical variant of angioedema.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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