

Angioedema in the Emergency Department: A Retrospective Cohort Study

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Introduction

- Angioedema can be life threatening, requiring prompt management when resulting in airway swelling and compromise.
- Angioedema can be histamine-mediated (i.e. anaphylaxis), bradykinin-mediated (medication-induced using angiotensin-converting enzyme inhibitors (ACEi) and dipeptidyl peptidase 4 inhibitors (DPP-4i), or genetic, such as hereditary angioedema.
- Bradykinin, a peptide involved in the kallikrein-kinin pathway, is inactivated by peptidase kininase II (ACE) and metabolized by DPP-4. Inhibition of this mechanism causes increased bradykinin levels, leading to vascular permeability, and therefore, angioedema.
- Bradykinin-mediated and histamine-mediated angioedema require different management, but they are frequently treated in the same manner.
- Studies suggest that the average time to a recurrent ACEi angioedema event for those who continue to take the offending agent is 11 months.
- Directed treatment for ACEi/DPP-4i induced angioedema is an active area of clinical investigation; various drugs currently indicated for hereditary angioedema, such as ecallantide, icatibant, C1-INH concentrates, and FFP have been proposed.
- The purpose of this study is to identify how patients admitted for angioedema are triaged and managed in the Emergency department, as well as to evaluate their discharge medication reconciliation in regards to discontinuing the offending agent.

Methods

- A retrospective cohort study was conducted investigating adults admitted to the ED for angioedema at a tertiary level university hospital.
- Data were abstracted from electronic medical records.
- Inclusion criteria: Age >18 years old, ICD10 Codes for Angioneurotic edema (T78.3)
- Exclusion criteria: Not meeting the criteria above
- 116 patients were included in the final sample.
- Statistical analysis: Chi-squared tests, Fisher's exact test. All reported p-values are 2-sided, and the significance cut-off was set at a value of 0.05. Data analyses were completed in R studio (R version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria).
- Outcome measures: Frequency of medication discontinuation, number of patients with angioedema taking ACEi/DPP-4i, treatment in the emergency department; disposition; readmission for angioedema within 1 week of discharge.

Results

Table 1: Patient Characteristics

Variable	Overall	N
Demographic		116
Age (mean (SD))	56.14 (17.83)	
Male (%)	48 (41.4)	
Race (%)		
Asian	7 (6.1)	
Black	45 (38.8)	
Hispanic	1 (0.9)	
White	34 (29.3)	
Other	29 (25.0)	
ICD.10 Angioedema	116 (100.0)	
Taking ACE-Inhibitor/DPP-4 Inhibitors (%)	52 (44.8)	
Etiology (%)^[1]		116
Drug	70 (60.4)	
Food	16 (13.8)	
Venom	2 (1.7)	
Hereditary Angioedema	3 (2.6)	
Environmental (Exercise)	1 (0.9)	
Unknown/Unclear	28 (23.2)	
Comorbidity (%)		116
Report has Non-Atopic Comorbidity	99 (83.6)	
Report has Atopic Comorbidity	42 (36.2)	
Diabetes	37 (31.9)	
Hypertension	76 (65.5)	
Hyperlipidemia	22 (19.0)	
Asthma	9 (7.8)	
Chronic Obstructive Pulmonary Disease (COPD)	6 (5.2)	
Allergy to Food/Medication/Hx of Allergic Rx	8 (6.9)	
Hypothyroidism	11 (9.5)	
Depression	6 (5.2)	
Atrial fibrillation	4 (3.4)	
Smoking Status		
Non-Smoker	66 (56.9)	
Smoker	25 (21.6)	
Unknown	25 (21.6)	
Admission (%)		116
Admitted by hospital	51 (44.0)	
Admitted Dept		51
MICU/CCU	17 (33.3)	
Inpatient	26 (51.0)	
Observation	8 (15.7)	
Readmitted	8 (7.0)	115
Readmitted within 1 week	7 (6.2)	112

^[1]Percentages may not add up to 100% because patients can have multiple etiologies for the angioedema. The percentage is calculated based on drug discontinuity of ACEi or DPP4i.

Table 2: Admission and Readmission Rates

Variables	Overall	ACEi/DPP4i		
		Not Currently on ACEi/DPP-4i	Currently on ACEi/DPP-4i	P Value
n	116	64	52	
Admitted (%)	51 (44.0)	24 (37.5)	27 (51.9)	0.17
Readmitted (%)	8 (7.0)	4 (6.2)	4 (7.8)	1.00
Readmitted within 1 week (%)	7 (6.2)	4 (6.5)	3 (6.0)	1.00

Table 3: Final Disposition

Variables	Overall	ACE/DPP4		
		Not Currently on ACEi/DPP-4i	Currently on ACEi/DPP-4i	P Value
n	51	24	27	
Admitted dept (%)				0.81
MICU/CCU	17 (33.3)	9 (37.5)	8 (29.6)	
Inpatient	26 (51.0)	11 (45.8)	15 (55.6)	
Observation	8 (15.7)	4 (16.7)	4 (14.8)	

Figure 1: Frequency of Medication Class Administered

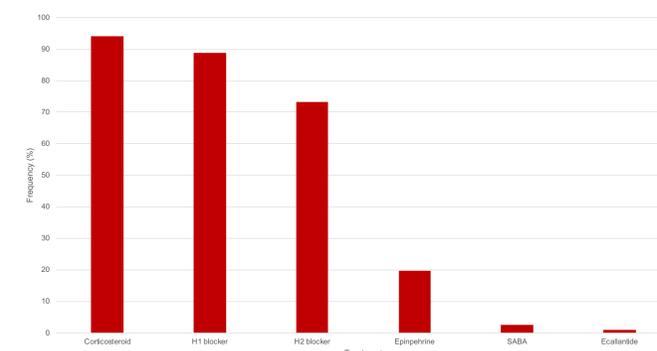


Table 4: Discontinuation of ACEi/DPP-4i by Angioedema Etiology

Angioedema Etiology ^[1]	ACEi and/or DPP4i		P Value
	Continued, N=13	Discontinued, N=39	
Drug, Freq (%)	12 (92.3)	38 (97.4)	0.53
Food, Freq (%)	1 (7.7)	2 (5.1)	
Unknown/unclear, Freq (%)	1 (7.7)	1 (2.6)	

^[1]Percentages may not add up to 100% because patients can have multiple etiologies for the angioedema. The percentage is calculated based on drug discontinuity of ACEi or DPP4i.

Table 5: Discontinuation of ACEi/DPP4i at Discharge

Medication Discontinuation	ACEi only N=50	DPP4i only N=8	ACEi and/or DPP4i N=52
Continue to use, Freq (%)	6 (12.0)	8 (100.0)	13 (25.0)
Discontinued, Freq (%)	44 (88.0)	0 (0.0)	39 (75.0)

Results (continued)

- 44.8% of patients who presented to the ED with a diagnosis of angioedema were taking ACEi and/or DPP-4i.
- While the admission rate for those on the medications was higher (51.9%), it was not statistically significant (p = 0.17).
- In terms of disposition, there was no significant difference in admission to ICU (33.3%), inpatient ward (51%) or observation unit (15.7%), p = 0.81.
- The readmission rate among those on ACEi/DPP-4i (42.8%) and those not (57.1%), was not statistically significant, p = 1.
- 0 % of patients presenting with suspected medication induced angioedema received treatment dedicated to bradykinin-mediated angioedema.
- 25% of these patients continued to use their medications after discharge.

Discussion

- In this population, close to half of the patients presenting to the emergency department with angioedema were taking ACE-inhibitors or DPP-4 inhibitors. About 25% of these patients with suspected medication induced angioedema continued to use their medication after discharge. This may be due to physician oversight or lack of patient education.
- The typical initial management of patients presenting with angioedema that includes antihistamines, steroids and epinephrine has not been shown to be effective in treating ACEi/DPP-4i mediated angioedema.
- For these specific patients, dedicated treatment for bradykinin-mediated angioedema should be considered after emergent stabilization. However, no patients on ACE-inhibitor or DPP-4 inhibitors received such targeted therapy in our study.
- Ecallantide, Icatibant, recombinant C1-INH concentrates, and FFP are potential therapies that block specific receptors in bradykinin-mediated angioedema pathways, and further research regarding these therapies need to be conducted, which may be why these therapies are not more commonly used.
- It is imperative that patients with suspected or confirmed ACEi/DPP-4i induced angioedema discontinue the offending medication(s) to avoid angioedema recurrence as standard of care.

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