



Knowledge and practice of Physicians towards Diagnosis and Emergency Treatment of Angioedema

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Abstract:

Background: Angioedema is an underdiagnosed illness with diagnostic and therapeutic challenges, characterized by episodic, sudden, and localized swelling of the skin and mucous membranes. It affects any area of the body and might be life-threatening. Physicians of different specialties may encounter angioedema patients in their daily practice. **Objective:** To assess physicians' knowledge and experience concerning diagnosis and emergency treatment of angioedema. **Methods:** we conducted an electronic survey involving 248 physicians of different specialties and degrees. The survey questions were designed to assess basic knowledge angioedema. The survey was distributed through online platforms and responses were collected

and analyzed. **Results.** Overall confidence reported by physicians regarding the evaluation of angioedema was 46.4% of participants, while only 34.3% had adequate practice about angioedema, 34.7% of physicians know the best definition of angioedema, 27% know the most suitable tests for diagnosis of a patient with suspected hereditary angioedema, 56.5% know the first step in emergency management of a patient with angioedema, 30.6 % of them know that adrenaline injection isn't mandatory treatment for all cases with angioedema and 27.8% know that antihistaminic drugs and corticosteroids are effective in allergic angioedema only. Emergency physicians and dermatologists had better practice about angioedema and 48.4% of physicians think that attending training on angioedema is important. **Conclusion:** there was insufficient baseline knowledge about angioedema and inadequate practice during dealing with such cases among physicians so training programs and educational courses would be of value to raise awareness of angioedema and improve its outcome.

Keywords: Angioedema, Emergency, Knowledge, Physicians

1. Introduction:

Angioedema is characterized by localized swelling of mucous membranes and skin, typically sudden and asymmetrical, resulting from a transient increase in plasma leakage and endothelial permeability in the submucosa and deep layers of the skin [1]. It often occurs alongside urticaria and usually resolves within a few hours or may persist for a few days. While it primarily affects the genital and loose facial skin, it can also impact the abdomen, airways, and extremities [2].

Angioedema is an increasing cause of hospitalizations; the incidence of

angioedema leads to approximately 80,000 to 112,000 emergency department visits each year, with 4 patients per 100,000 population requiring admission. Angioedema can have various causes, including allergic reactions, hereditary factors, acquired conditions, and idiopathic origins [3].

Angioedema is divided according to pathophysiology into a histaminergic form that occurs with an allergy to food, venom, latex, and medication or may be a part of acute or chronic spontaneous urticaria and non-histaminergic (bradykinin mediated) forms which comprise several forms of

hereditary or acquired C1 esterase inhibitor deficiency, idiopathic, and drug-induced angioedema. Histamine and bradykinin are the most important mediators of angioedema. The suitable treatment is determined by clinical presentation and frequency of attacks which can help to guide physicians toward the triggering mediator [4].

Angioedema is usually diagnosed clinically based on history and physical findings in the Emergency Department (ED) and immediate intervention should be started as soon as possible, then Laboratory investigations can be done later. If hereditary angioedema is suspected, then measuring C4 and C1 esterase inhibitor (C1-INH) levels is beneficial [5]. The most important step in ED management is the assessment of the airway patency and evaluation for anaphylaxis. In the case of acute histaminergic angioedema medical treatment consists of antihistaminic, corticosteroid injections and inhalation of nebulized adrenaline for laryngeal edema and possibly intramuscular adrenaline for anaphylactic shock [6]. In the acute phase of bradykinin-related angioedema adrenaline isn't effective for such cases so specific drugs may be needed including, C1INH concentrate, bradykinin receptor-2 antagonist (Icatibant) or Kallikrein inhibitor (Ecallantide). Fresh frozen plasma is also

used if the above drugs aren't available [7]. Discharge of Patients who received the specific therapy can be done when symptoms start to be improved. If angioedema symptoms are worsening despite usual medications or the diagnosis is still unclear, the patient should be referred to a specialized center especially if C1 inhibitor deficiency is suspected [8].

The current study aimed to assess physicians' knowledge and experience concerning diagnosis and emergency treatment of angioedema.

2. Patients and methods:

Study design

This cross-sectional study was conducted over a 5-month period, from January 2023 to May 2023. The study included physicians from various healthcare settings in Egypt. Approximately fifty percent of the physicians were employed at Menoufia University hospitals, while the remaining physicians worked in different types of hospitals, including general hospitals, teaching hospitals, private hospitals, chest hospitals, fever hospitals, and primary health units. These healthcare facilities were in different governorates across Egypt. All participants agreed to participate and were assured of the

confidentiality of their responses. The study followed the ethical standards of our institution. Informed consent from all participants was obtained under the local ethical committee.

Participants

Physicians who met the following criteria were included in the study; they had to answer all the questions in the survey, be between the ages of 24 and 60, and be from any medical specialty, regardless of their level of experience. However, medical students, as well as physicians under the age of 24 or above the age of 60 and who did not answer all the questions, were excluded from the study. Medical specialties of participants include general internal medicine, pediatrics, Nephrology, cardiology, chest, GIT, Rheumatology and immunology, Hematology and dermatology. Surgical specialties include General Surgery, Neurosurgery, Cardiothoracic surgery, Urology, Vascular, Orthopedic, Ophthalmology, ENT, Obstetrics and Gynecology. Primary care units include Health units and outpatient clinics. Secondary care includes general and private hospitals. Tertiary care hospitals include teaching, university, and specialized hospitals (fever, eye hospitals).

Survey tools

The study was conducted using an electronic-based survey consisting of thirty-nine questions to assess physicians' knowledge and practice related to angioedema. The survey was distributed through social media platforms and email, and the responses were collected using an electronic excel sheet. The structured questionnaire was divided into three parts: Part I was concerned with the socio-demographic characteristics of the participants including age, gender, governate, place of work, specialty, profession, and years of experience. Part II was used to assess practitioners' knowledge of angioedema. This was done through nine questions that covered various aspects of the disease, including the number of cases they had dealt with before, the type of angioedema they commonly encountered, the presentation of angioedema, the ability to suspect angioedema, the level of confidence during its evaluation and management, previous training in angioedema, and experience in handling angioedema cases. Participants were allowed to select more than one answer for this part of the survey. physicians who answered four or more questions (60% or more fair answer) were categorized as having good practice. Part III of the survey was used to assess knowledge about angioedema, and divided

into two sections: Section A assessed physicians' knowledge about the pathology of angioedema in the form of Ten questions about the definition, causes of the disease, most common drug to cause angioedema, causes of hereditary angioedema, clinical features related to angioedema, body areas affected, history taking, edema, the criteria of bradykinin-mediated angioedema, and the outcome of the disease. Participants were allowed to select more than one answer for each question. Section B: assessed knowledge about diagnosis and treatment of angioedema in the form of eleven questions about the most suitable diagnostic tests for a patient with suspected hereditary angioedema, the screening test of choice for hereditary angioedema, the screening test of choice for allergic angioedema, the first step in the emergency evaluation and management of a patient with angioedema, Adrenaline, Antihistaminic drugs, corticosteroids, effective drugs in treating acute phase of bradykinin related angioedema, prophylactic treatment for hereditary angioedema, prophylactic treatment for allergic angioedema, prophylaxis of recurrence of attacks, drugs used for prophylaxis and contraindicated in pregnant women. The last question was a comment about this questionnaire [9]. The

best answers were scored as one point, while other options were scored as zero points. The total knowledge scores ranged from 0 to 22. The researchers establish knowledge levels by using a cutoff point that separates scores above and below 60% of the best responses. (answered ≥ 13 question correctly), so physicians who scored \geq sixty percent were considered to have a high level of knowledge, and those scoring below sixty percent were considered to have a low level of knowledge.

Statistical Analysis:

The data was analyzed using the Statistical Package for Social Science program version 20 (SPSS; Inc., Chicago, IL, USA). Qualitative variables, such as age categories and gender....etc. were described in frequencies. On the other hand, continuous data, such as practice and knowledge scores, were described as the mean and standard deviation. The Chi square Test was used for testing the association or relationship between two or more dichotomous categorical variables. Fisher's exact test is a non-parametric test for testing independence that is typically used only for 2x2 contingency table. The Kruskal-Wallis's test is nonparametric test that used to determine if there were statistically significant differences between two or more groups of an

independent variable on a continuous or ordinal dependent variable (the angioedema practice level and knowledge score. The Pearson's correlation is a measure of the

strength and direction of association that exists between two variables measured on at least an interval scale (angioedema practice and knowledge scores).

3. Results:

Table (1): Demographic data of participants

Parameter	Frequency 248	Percent 100.0 %
Age		
Less than 25 years	27	10.9
25-35 years	154	62.1
Above 35 years	67	27
Gender		
Female	138	55.6
Male	110	44.4
Professional degree		
Intern/house officer	37	14.9
Resident	74	29.8
Specialist	105	42.3
Consultant	32	12.9
Specialty		
Intern/ General Practitioner	22	8.9
Medicine specialties	128	51.6
Surgical specialties	65	26.2
Emergency/ critical care	33	13.3
Place of work		
Primary care units	13	5.2
Secondary care hospitals	53	21.3
Tertiary care hospitals	182	73.5
Years of experience		
Less than 2 years	41	16.5
2-10 years	151	60.9
More than 10 years	56	22.6
Number of angioedema cases dealt with		
Never	155	62.5
1-10	74	29.8
11-20	9	3.6
More than 20	10	4.0

ICU: intensive care unit

This Table showed: Physicians were distributed according to different parameters as we noticed that the majority of them were between age of 25-35y (62.1%), females (55.6%) specialists (42.3%), specialized in medicine specialties (51.6%), worked in Tertiary care hospitals (73.5%), had 2-10 years of experience (60.9%), and hadn't dealt with any cases of Angioedema before (62.5%).

Table (2): Comparison between physicians according to the level of Practice

Parameter	Practice of angioedema		X ² (P value)	OR (LL – UL 95% C.I)
	Adequate practice	Insufficient practice		
	NO 85 (34.3%)	NO 163 (65.7%)		
Age				
< 25y	2(2.3)	25(15.3)	11.067 (0.004)	10.33(2.16-49.29)* 1.48(0.75-2.93)
26- 34y	64(75.3)	115(70.5)		
≥35y	19(22.4)	23(14.1)		
Specialty				
Intern/ GP	2(2.4)	20(8.9)	21.408 (<0.001)	10.62(2.13-52.9) * 1.5(0.70-3.23) 5.43(2.02-14.58) *
Medical specialties	57(67.1)	81(49.7)		
Surgical specialties	9(10.6)	46(28.2)		
Emergency/ Critical care	17(20.0)	16(9.8)		
Place of work				
Primary care units	2(2.4)	11(6.7)	3.337 (0.189)	-----
General hospitals	22(25.9)	31(19.0)		
Tertiary care hospitals	61(71.8)	121(74.2)		
Years of experience				
Less than 2 years	9(10.6)	31(19.0)	4.293 (0.117)	-----
2-10 years	52(61.2)	100(61.3)		
More than 10 years	24(28.2)	32(19.6)		
Dealt with angioedema cases.				
Never	42(49.4)	113(69.3)	9.452 (0.002)	2.31(1.34-3.97) *
Deal before	43(50.6)	50(30.7)		

OR: Odds ratio χ^2 : Chi square test ®: Reference group

Z: Kruskal-Wallis test

CI: Confidence interval LL: Lower limit UL: Upper Limit

*: Statistically significant at p ≤ 0.05

This Table showed: There were significant differences between angioedema practice and age (P value < 0.001), specialty (P value < 0.001) and whether dealt with angioedema cases before (P value < 0.001) as 17.6% the studied physician aged less than 25 years old had inadequate angioedema practice (odds = 10.33, confidence interval 2.16-49.29). In addition, 11.1% of intern/ GP physicians (odds = 10.62, confidence interval 2.13-52.9) and 38.8% of the studied surgeons (odds = 5.43, confidence interval 2.02-14.58) were with inadequate practice level. Most of the studied physicians (69.3%) who never dealt before with angioedema cases were of inadequate practice (odds = 2.31, confidence interval 1.34-3.97). there was significant difference between knowledge level and angioedema practice (P value = 0.019) as the 91.4% of physicians with unsatisfactory knowledge were with insufficient angioedema practice with odds 2.467 and confidence interval (1.14-5.341).

Table (3): Comparison between physicians according to the level of knowledge

Parameter	knowledge of angioedema		χ ² (P value)	OR (LL – UL 95% C.I)
	Satisfactory	Unsatisfactory		
	NO 30 (12.1%)	NO 218 (87.9%)		
Age				
< 25 years	3(10.0)	24(11.0)	0.311 (0.856)	-----
25-34 years	20(66.7)	134(61.5)		
≥35 years	7(23.3)	60 (27.5)		
Gender				
Female	23(76.7)	158(72.5)	0.235 (0.628)	-----
Male	7(23.3)	60(27.5)		
Professional degree				
Intern/house officer	1(2.7)	36(97.3)	4.949 (0.176)	-----
Resident	9(12.2)	65(87.8)		
Specialist	17(16.2)	88(83.8)		
Consultant	3(9.4)	29(90.6)		
Specialty				
Intern/ GP	3(10.0)	19(8.7)	3.079 (0.380)	-----
Medical specialist	20(66.7)	118(54.1)		
Surgical specialist	3(10.0)	52(23.9)		
Emergency/ critical care	4(13.3)	29(13.3)		
Place of work				
Primary care units	3(10.0)	10(4.6)	2.556	-----
General hospitals	4(13.3)	49(22.5)		
Tertiary care hospitals	23(76.7)	159(72.9)		

Years of experience, years				
Less than 2 years	3(10.0)	37(16.9)	0.964 (0.617)	----
2-10 years	20(66.7)	132(60.6)		
More than 10	7(23.3)	49(22.5)		
Angioedema cases dealt.				
Never	1(3.3)	154(70.6)	50.975 (<0.001)	69.78 (9.31-523.25)
Yes, dealt before	29(96.7)	64(29.4)		
Level of knowledge				
adequate	16(53.3)	69(31.7)	5.503 (0.019)	2.467 (1.14-5.34)
insufficient	14(46.7)	149(68.3)		

OR: Odds ratio χ^2 : Chi square test
 CI: Confidence interval LL: Lower limit UL: Upper Limit
 *: Statistically significant at $p \leq 0.05$

This Table showed: There were significant differences between angioedema knowledge and practice score (P value = 0.019) and dealing with angioedema cases before (P value < 0.001) as 68.3% the studied physician with inadequate angioedema practice had unsatisfactory angioedema knowledge. Physicians with perfect practice level are predicted to have good knowledge (odds = 2.467, confidence interval 1.14-5.34). Whether 70.6% of the studied physicians who never dealt with angioedema cases before were with unsatisfactory angioedema knowledge. So, the physician who dealt with angioedema cases before predicted to have good knowledge (odds = 69.78, confidence interval 9.31-523.25). Age groups, gender, professional degree, specialty, place of work, years of experience, didn't differ significantly (P value = 0.05) with knowledge level.

Table (4): Reported Practice aspects regarding angioedema among the studied physicians

Parameter	Adequate practice (total number 248)	Percent 100.0 %
Suspecting the presence of angioedema in patients describing swelling and allergy	98	39.5
Confidence in the evaluation and management of angioedema	115	46.4
Previous education and training provide sufficient information about angioedema	88	35.5
The experience for angioedema diagnosis	52	21.0
The experience for treatment of angioedema	121	48.8
Request any investigations to diagnose angioedema	37	14.9
Importance of attending a training/workshop on angioedema	120	48.4
Practice score		
Mean ±SD	2.54±2.37	
Min- Max.	0.0-7.0	
Practice level *		
adequate	85	34.3
insufficient	163	65.7

* Adequate practice when practice score 4 or more (60% of best answers)

This Table showed: In assessment of Practice of physicians about angioedema according to different parameters; Only 39.5% of physicians suspect the presence of angioedema in patients describing swelling and allergy while 64.6% of them are Confidant in the evaluation and management of angioedema. Although 35.5% of physicians have sufficient information about angioedema via their previous education and training, only 21% of physicians have experience for angioedema diagnosis and 48.8% have experience for treatment of angioedema. 14.8% of physicians requested investigations to diagnose angioedema .48.4% of physicians think that attending a training or workshop on angioedema is important. Only 34.3%of physicians have overall adequate practice about angioedema while the rest of them (65.7%) have inadequate practice.

Table (5): Knowledge about angioedema disease, diagnosis, and treatment among the studied physicians

Parameter	Best answer choice (total number 248)	Percent 100.0 %
Definition of angioedema	86	34.7
Causes of angioedema	28	11.3
The most likely medication to cause angioedema	69	27.8
HAE is an autosomal dominant disorder caused by deficiency or dysfunction of C1 inhibitors	51	20.6
The clinical features related to angioedema	7	2.8
Areas of the body might be affected by angioedema	97	39.1
The most important item to ask in the interview of patient with suspected hereditary angioedema	84	33.9
The most important items to ask in the interview of patient with angioedema	17	6.9
Characters of Bradykinin mediated angioedema	47	19.0
The outcome of angioedema	17	6.9
The most suitable for the diagnosis of a patient with suspected hereditary angioedema	67	27.0
The screening test of choice for hereditary angioedema	43	17.3
The screening test of choice for allergic angioedema	115	46.4
The first step in emergency evaluation and management of a patient with angioedema	140	56.5
Whether adrenaline injection is mandatory treatment for all cases with angioedema	76	30.6
Antihistaminic drugs and corticosteroids are effective drugs in which type of angioedema	69	27.8
Which drugs are effective in treating acute phase of bradykinin related angioedema	58	23.4
A Prophylactic treatment for hereditary angioedema	13	5.2
The best drugs used for prophylaxis of allergic angioedema	92	37.1
Whether avoidance of medications that triggers of angioedema is important in prophylaxis of recurrence of attacks	100	40.3
Whether drugs used to treat hereditary angioedema is contraindicated in women who are pregnant prophylaxis	79	31.9

This Table showed Regarding the knowledge about various aspects of angioedema; 34.7% of physicians know the best definition of angioedema while 11.3% of them know causes of the disease. Although 27.8% of physicians know the most likely medication to cause angioedema, only 20.6% of them knows the cause of HAE. In despite of 2.8% of physicians know the clinical features related to angioedema, 39.1% of them know Areas of the body might affected by angioedema. Only 6.9% of physicians know the most important items to ask in the interview of patient with angioedema while 19% of them know Characters features of bradykinin mediated angioedema. Few number of physicians (6.9%) know the outcome of angioedema. Only 27% of physicians know the most suitable tests for diagnosis of a patient with suspected hereditary angioedema. 17.3% of physicians know the screening test of choice for hereditary angioedema while 46.4% of them know the screening test of choice for allergic angioedema. 56.5% of physicians know the first step in emergency evaluation and management of a patient with angioedema, but 30.6 % of them know that adrenaline injection isn't mandatory treatment for all cases with angioedema. 27.8% of physicians know that Antihistaminic drugs and

corticosteroids are effective drugs in which type of angioedema. Only 23.4% of physicians know Which drugs are effective in treating acute phase of bradykinin related angioedema while 5.2% of them know Prophylactic treatment for hereditary angioedema. 37.1% of physicians know the best drugs used for prophylaxis of allergic angioedema but 40.3% of them know Whether avoidance of medications that triggers of angioedema is important in prophylaxis of recurrence of attacks or not. 31.9% of physicians know Which drug used to treat hereditary angioedema is contraindicated in women who are pregnant.

4. Discussion:

Angioedema is an underdiagnosed illness, It is usually a benign and transient condition, but it can be life-threatening if causing airway obstruction. Its treatment is determined according to the underlying mechanism, severity, and acuity [10].

In this study, it was concluded that about two-thirds of the studied physicians (65.7%) had inadequate practice regarding angioedema. This finding is similar to the study done by Zanichelli et al that reported that there was a delay in diagnosis between HAE patients in eight European countries of about 8.5 years

due to low awareness of HAE among physicians. [11].

Concerning the relationship between practice level of angioedema and age, we noticed in this study there was a statistically significant relationship. Inadequate angioedema practice was more prevalent in younger physicians.

This finding agrees with Grossman et al who performed a survey on 1114 physicians specialized in pediatric emergency medicine about their practice and knowledge about anaphylaxis. They concluded that older physicians with more years of experience had better practice than younger physicians [12].

On the other hand, this finding was different with Iwamoto et al who conducted a survey in Japan about HAE diagnosis and treatment. They concluded that there was a little difference between young and old physicians regarding the level of awareness about HAE. This difference in findings might be due to differences in the study participants or methodology, or variations in the prevalence of HAE and the level of knowledge and education about the disease in different regions [13].

Our study found a significant relationship between the level of practice regarding angioedema and medical specialty. Dermatologists and emergency medicine

physicians had better practice about angioedema compared to other medical specialties.

This finding resembles Atsushi et al who performed a web-based survey in Japan about physicians' awareness and understanding of HAE. They concluded that There were different levels of knowledge of HAE among medical specialties e.g., surgeons, and internal medicine physicians had lower awareness than physicians in other medical specialties, but emergency medicine physicians, Dermatologists, and pediatricians had a higher level of knowledge about HAE due to the association of symptoms with their specialty [14].

Our study found no significant relationship between the level of practice regarding angioedema and years of experience in the physicians we studied. This finding differs from that of González-Díaz et al, who conducted a survey on 1023 healthcare providers. They observed that physicians with 30 years of experience or more had a higher percentage of best answers compared to physicians with fewer years of experience. [15].

Our study found a significant relationship between the level of practice regarding angioedema and prior experience with such

cases, with physicians who had never dealt with angioedema cases before demonstrating inadequate practice about the disease.

This finding agreed with Mete et al who surveyed 155 physicians and reported that about 7.3% of physicians had never heard about HAE, and 84% of participants didn't know any laboratory tests that were used for diagnosis of HAE. Also, only 10% of physicians had some information about C1 esterase inhibitor, so they concluded that there was a lack of awareness and knowledge regarding the disease among physicians who had not dealt with it before [16].

The current study concluded that 87.9% of physicians had incomplete knowledge about the disease pathology of angioedema. This finding is consistent with Riedl et al who performed a study on the current medical management of hereditary angioedema among US physicians. They reported that there was a delay between the onset of symptoms and diagnosis of AE of a mean period of seven years due to the lack of physician knowledge about the disease throughout the world because of its rarity. These findings highlight the need for increased education and awareness among physicians regarding the pathology and

management of angioedema to improve disease outcomes [17].

Regarding knowledge about diagnosis and treatment of angioedema among the studied physicians in our study, we concluded that a significant proportion of physicians had unsatisfactory knowledge regarding the diagnosis and treatment of angioedema with 77.8% of physicians demonstrating inadequate knowledge in this field. Additionally, the overall level of knowledge about angioedema among the studied physicians was found to be unsatisfactory with 88% of physicians having adequate knowledge of the condition.

These findings are like Mete et al who concluded that physicians from different specialties couldn't differentiate between allergic angioedema, and HAE leading to incorrect approaches and treatment. This highlights the need for increased education and awareness among physicians regarding the accurate diagnosis and appropriate treatment of angioedema to improve patient outcomes [18].

5. Conclusion:

Our study reveals a concerning insufficient knowledge and inadequate practice among physicians about angioedema. This implies a

potential risk for delayed diagnosis and suboptimal management of angioedema cases. Periodic Educational activities and more training programs for physicians should be done to improve their knowledge and practice about angioedema.

List of abbreviations:

AE: Angioedema, **C1-INH:** C1 esterase inhibitor, **HAE:** Hereditary angioedema **NSAIDs:** Non-steroidal anti-inflammatory drugs, **Ig E:** Immunoglobulin E, **ED:** Emergency Department,

Supplementary data: survey questions were attached.

6. References:

1. Zuberbier T, Balke M, Worm M et al. Epidemiology of urticaria: a representative cross-sectional population survey. *Clin Exp Dermatol.* 2010; 35: 869 – 73.
2. Frigas E, Park M. Idiopathic recurrent angioedema. *Immunol Allergy Clin North Am.* 2006; 26: 739 – 51.
3. Zanichelli A, Arcolego F, and Barca MP. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis.* 2015; 10:11.
4. Cicardi M, Suffritti C, Perego F, and Caccia S. Novelties in the Diagnosis and Treatment of Angioedema. *J Investig Allergol Clin Immunol.* 2016; Vol. 26(4): 212-221 doi: 10.18176/jiaci.0087.
5. Wilkerson RG. Angioedema in the emergency department: an evidence-based review. *Emerg Med Pract.* 2012; 14 (11):1-21.
6. James C and Bernstein JA. Current and future therapies for the treatment of histamine-induced angioedema. *Expert Opin Pharmacother.* 2017; 18(3):253-62.
7. Bas M, Hoffmann TK, Bier H, and Kojda G. Increased C-reactive protein in ACE-inhibitor-induced angioedema. *Br J Clin Pharmacol.* 2005; 59:233.
8. Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, Caballero T, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy.* 2014;69:602-16
9. Sibabratta Patnaik, Samarth Krishna, and Mukesh Kumar Jain. Knowledge, Attitude, and Practice regarding Anaphylaxis among Pediatric Health Care Providers in a Teaching Hospital. *Journal of Child Science.* 2020; 10(01): e224-e229.

10. Ring J, Beyer K, and Biedermann T. Guideline for acute therapy and management of anaphylaxis. *Allergo J Int.* 2014; 23: 96–112.
11. Zanichelli A, Magerl M, Longhurst H, Fabien V, and Maurer M. Hereditary angioedema with C1 inhibitor deficiency: delay in diagnosis in Europe. *Allergy Asthma Clin Immunol.* 2013; 9:29.
12. Grossman SL, Baumann BM, Garcia Peña BM, Linares MY, Greenberg B, and Hernandez-Trujillo VP. Anaphylaxis knowledge and practice preferences of pediatric emergency medicine physicians: a national survey. *J Pediatr.* 2013; 163 (03):841–846.
13. Iwamoto K, Yamamoto B, Ohsawa I, Honda D, Horiuchi T, and Tanaka A. The diagnosis and treatment of hereditary angioedema patients in Japan: a patient reported outcome survey. *Allergol Int.* 2021; 70(2):235–43.
14. Atsushi Fukunaga, Miwa Kishimoto, Akinori, Takeshi Akiyama, Ippei Kotera, Yoichi Inoue, et al. Physician awareness and understanding of hereditary angioedema: A web-based study in Japan. *J Cutan Immunol Allergy.* 2022; 5:158–169.
15. González-Díaz SN, Villarreal-González RV, Fuentes-Lara EI, Salinas-Díaz MDR, de Lira-Quezada CE, Macouzet-Sánchez C, et al. Knowledge of healthcare providers in the management of anaphylaxis. *World Allergy Organ J* 2021;14(11):100599
16. Mete GN, Gülbahar O, Koç PZ, Büyüköztürk S, Sin AZ, Gelincik A, et al. How familiar are internists with a potentially deadly orphan disease? Hereditary Angioedema. *Turk Klin Tip Bilim Derg.* 2015; 35:67-72.
17. Riedl M, Gower RG, and Chrvala CA. Current medical management of hereditary angioedema: results from a large survey of US physicians. *Ann Allergy Asthma Immunol.* 2011; 106:316-22.e4.
18. Mete Gökmen N, Gülbahar O, Onay H, Peker Koc Z, Özgül S, Köse T, et al. Deletions in SERPING1 lead to lower C1 inhibitor function: lower C1 inhibitor function can predict disease severity. *Int Arch Allergy Immunol.* 2019; 178:50-9.