Clinical Practice Statement:

What is the Emergency Department Management of Patients with Angioedema Secondary to an ACE-inhibitor? (4/11/2011)

2. Literature Search

A literature search of the National Library of Medicine's MEDLINE database's PubMed system was performed and limited to human studies written in the English language. Keywords used in the search included: angioedema, ACE-inhibitors, corticosteroids, antihistamines, epinephrine, laryngoscopy, and intubation. The findings of this search are noted in Table 1. Combining the references resulted in 562 articles on angioedema and ACE-inhibitors.

Two physicians independently reviewed the titles of these 562 articles. A total of 27 articles were deemed appropriate for review based upon their relevance to the clinical question. These 27 articles included randomized controlled trials, prospective trials, retrospective cohort studies, case series and case reports. General review articles were not included for formal review. These 27 references are listed in Table 1 under the column heading of "References for Final Review".

Table 1: Human Studies Written in English Language

Search Parameter	**All References**	**References for Final Review**
Angioedema and ACE inhibitors; systematic reviews	8	0
Angioedema and ACE inhibitors; randomized controlled trials, core clinical journals	6	1
Angioedema and ACE inhibitors; randomized controlled trials	15	1
Angioedema and ACE inhibitors; clinical trials	22	3
Angioedema and ACE inhibitors	448	14
Angioedema and ACE inhibitors and corticosteroids	22	2
Angioedema and ACE inhibitors and antihistamines	35	3
Angioedema and ACE inhibitors epinephrine	23	0
Angioedema and ACE inhibitors and	2	0

laryngoscopy		
Angioedema and ACE inhibitors and intubation	29	3

3. Final Evidence Database – Grade of Evidence

For each of the 27 articles subjected to detailed review, the evidence was assigned a grade using reference focus, design, and methodology.

Grade A	Randomized clinical trial or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials) directly addressing the review issue
Grade B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials) indirectly addressing the review issue
Grade C	Prospective, controlled, non-randomized, cohort studies
Grade D	Retrospective, non-randomized, cohort or case-control studies
Grade E	Case series, animal/model scientific investigations, theoretical analyses, or case reports

4. Final Evidence Database – Quality Ranking

Each of the 27 articles subjected to detailed review was assessed to design and methodology. This includes Design Consideration (focus, model, structure, presence of controls, etc.) and Methodology Consideration (actual methodology utilized).

Ranking	**Design Consideration Present**	**Methodology Consideration Present**	**Both Considerations present**
Outstanding	Appropriate	Appropriate	Yes, both present
Good	Appropriate	Appropriate	No, either present
Adequate	Adequate with possible bias	Adequate	No, either present
Poor	Limited or Biased	Limited	No, either present
Unsatisfactory	Questionable/None	Questionable/None	No, either present

	Article	**Grade**	**Quality**	**Design/Size**
1	Kostis JB, et al. Incidence and characteristics of angioedema associated with enalapril. Arch Intern Med. 2005 Jul 25;165(14):1637-42.	B	Adequate	Randomized, double blind controlled trial (12,557 patients)
2	Piller LB, et al.			

	Incidence and predictors of angioedema in elderly hypertensive patients at high risk for cardiovascular disease: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens (Greenwich). 2006 Sep;8(9):649-56	B	Good	Randomized, controlled trial (42,418 patients)
3	Bas M, et al. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: a case series. Ann Emerg Med. 2010 Sep;56(3):278-82. Epub 2010 May 5.	C	Poor	Prospective Cohort (8 patients)
4	Banerji A, et al. Multicenter study of patients with angiotensin-converting enzyme inhibitor-induced angioedema who present to the emergency department. Ann Allergy Asthma Immunol. 2008 Apr;100(4):327-32.	D	Adequate	Retrospective Cohort (220 cases)
5	Chiu AG, et al. Angiotensin-converting enzyme inhibitor-induced angioedema: a multicenter review and an algorithm for airway management. Ann Otol Rhinol Laryngol. 2001	D	Adequate	Retrospective Cohort (108 patients)

	Sep;110(9):834-40.			
6	Hussain N, et al. A case of airway compromise. BMJ. 2010 Sep 29;341:c3822.	E	Poor	Case Report
7	Bluestein HM, et al. Angiotensin-converting enzyme inhibitor-induced angioedema in a community hospital emergency department. Ann Allergy Asthma Immunol. 2009 Dec;103(6):502-7.	D	Poor	Retrospective Cohort (140 patients)
8	Saxena S, et al. Supraglottic swelling may not correlate with tongue swelling in angiotensin converting enzyme inhibitor-induced angioedema. Laryngoscope. 2010 Jan;120(1):62-4.	E	Adequate	Case Report
9	Roberts DS, et al. Analysis of recurrent angiotensin converting enzyme inhibitor-induced angioedema. Laryngoscope. 2008 Dec;118(12):2115-20.	D	Adequate	Retrospective Cohort (692 patients)
10	Hill C, et al. Retrograde intubation for ace inhibitor-induced angioedema. Acad Emerg Med. 2008 Aug;15(8):791.	E	Unsatisfactory	Case Report
11	Grant NN, et al. Clinical experience with angiotensin-converting enzyme inhibitor-induced angioedema. Otolaryngol Head Neck Surg. 2007	D	Adequate	Retrospective Cohort (228 patients)

	Dec;137(6):931-5.			
12	Malde B, et al. Investigation of angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Ann Allergy Asthma Immunol. 2007	D	Unsatisfactory	Retrospective Cohort (64 patients)
13	Sondhi D, et al. Airway compromise due to angiotensin-converting enzyme inhibitor-induced angioedema: clinical experience at a large community teaching hospital. Chest. 2004 Aug;126(2):400-4.	D	Poor	Retrospective Cohort (70 patients)
14	Warrier MR, et al. Fresh frozen plasma in the treatment of resistant angiotensin-converting enzyme inhibitor angioedema. Ann Allergy Asthma Immunol. 2004 May;92(5):573-5.	D	Unsatisfactory	Case Report
15	Nadel ES, et al. Angioedema. J Emerg Med. 1998 May-Jun;16(3):477-9.	E	Unsatisfactory	Case Report
16	Brown NJ, et al. Recurrent angiotensin-converting enzyme inhibitor--associated angioedema. JAMA. 1997 Jul 16;278(3):232-3	D	Poor	Retrospective Cohort (82 patients)
17	Agah R, et al. Angioedema: the role of ACE inhibitors and factors associated with poor clinical outcome.	D	Adequate	Retrospective Cohort (40 patients)

	Intensive Care Med. 1997 Jul;23(7):793-6.			
18	Gabb GM, et al. Epidemiological study of angioedema and ACE inhibitors. Aust N Z J Med. 1996 Dec;26(6):777-82.	D	Poor	Retrospective Cohort (48 patients)
19	Cohen EG, et al. Changing trends in angioedema. Ann Otol Rhinol Laryngol. 2001 Aug;110(8):701-6.	D	Unsatisfactory	Retrospective Cohort (64 patients)
20	Thompson T, et al. Drug-induced, life-threatening angioedema revisited. Laryngoscope. 1993 Jan;103(1 Pt 1):10-2.	D	Unsatisfactory	Retrospective Cohort (36 patients)
21	Nielsen EW, et al. Angioedema from angiotensin-converting enzyme (ACE) inhibitor treated with complement 1 (C1) inhibitor concentrate. Acta Anaesthesiol Scand. 2006 Jan;50(1):120-2.	E	Poor	Case Report
22	Seidman MD, et al. Angioedema related to angiotensin-converting enzyme inhibitors. Otolaryngol Head Neck Surg. 1990 Jun;102(6):727-31.	E	Adequate	Case Series (6 patients)
23	Gianos ME, et al. Enalapril induced angioedema. Am J Emerg Med. 1990 Mar;8(2):124-6.	E	Unsatisfactory	Case Series (3 patients)
24	Banerji A, et al. Ten-year study of causes of moderate to severe angioedema seen by an inpatient	D	Adequate	Retrospective Cohort (69 patients)

	allergy/immunology consult service. Allergy Asthma Proc. 2008 Jan-Feb;29(1):88-92.			
25	Megerian CA, et al. 5 years' experience, with a review of the disorder's presentation and treatment. Laryngoscope. 1992 Mar;102(3):256-60.	D	Poor	Case Series (17 patients)
26	Roberts JR, et al. Clinical characteristics of angiotensin-converting enzyme inhibitor-induced angioedema. Ann Emerg Med. 1991 May;20(5):555-8.	E	Poor	Case Series (2 patients)
27	Bentsianov BL, et al. The role of fiberoptic nasopharyngoscopy in the management of the acute airway in angioneurotic edema. Laryngoscope. 2000;110:2016-2019	D	Adequate	Case Series (70 patients)

5. Assign the Reference Support of the Question

Independent review of the articles, as well as discussion, by the authors was undertaken to answer our clinical question. The references were sorted into 3 categories; supportive, neutral, and opposed. There were no neutral or opposed references for this clinical question. Table 2 lists the supportive references along with the appropriate location using both Grade and Quality of Evidence.

Table 2

Quality/Grade	A	B	C	D	E
Outstanding					
Good		2			
Adequate		1		4, 5, 9, 11, 17 24, 27	8, 22
Poor			3	7, 13, 16, 18, 25	6, 21, 26
Unsatisfactory				12, 14, 19, 20	10, 15, 23

6. Recommendations

Level of Recommendation	Criteria for Level of Recommendation	Mandatory Evidence
Class A Recommended with outstanding evidence	Acceptable Safe useful Established/definitive	Level A/B grade Outstanding quality Robust All positive
Class B Acceptable and appropriate with good evidence	Acceptable Safe Useful Not yet definitive	Level A/B grade lacking Adequate to good quality Most evidence positive No evidence of harm
Class B1	Standard approach	Higher grades of evidence Consistently positive
Class B2	Optional or alternative approach	Lower grades of evidence Generally but not consistently positive
Class C Not acceptable or not appropriate	Unacceptable Unsafe Not useful	No positive evidence Evidence of harm
Class Indeterminate Unknown	Minimal to no evidence	Minimal to no evidence

Background

ACE-inhibitors have become one of the most prescribed medications worldwide.[1, 2] Angioedema is a well-recognized adverse effect of this class of medications. The reported incidence of ACE-inhibitor angioedema ranges from 0.1% to 1.0%.[3] Importantly, ACE-inhibitor angioedema is a class effect and is not dose-dependent.[1] Symptoms can occur anywhere from a few hours up to 10 years after the initial dose. In fact, up to 40% of patients with ACE-inhibitor angioedema present months to years after their initial dose.[3]

The pathophysiology of ACE-inhibitor angioedema remains controversial. Decreased degradation of bradykinin, a potent vasodilator that increases vascular permeability, is believed by many to be the primary pathophysiologic process for ACE-inhibitor induced angioedema. C1-inhibitor abnormalities, carboxyalkydipeptide N, urinary kallikrein, and inflammatory mediators such as interleukin-1 and tumor necrosis factor have also been proposed as mediators for ACE-inhibitor angioedema.[3, 4]

Goals

Patients with ACE-inhibitor angioedema generally present to an emergency department (ED) for evaluation and treatment. As such, the emergency physician must be expert at evaluating and managing this potentially life-

threatening condition. The primary goal of this literature search was to determine the appropriate ED management of patients with ACE-inhibitor angioedema. Specific focus was given to the use of medications, such as corticosteroids and antihistamines, the role of fiberoptic examination, and criteria for ED patient observation and hospital admission.

Recommendation: Diagnosing ACE-inhibitor Angioedema

Angioedema is characterized by the abrupt onset of non-pitting, non-pruritic swelling that involves the reticular dermis, subcutaneous, and submucosal layers.[1, 5, 6] Lesions are typically asymmetric in distribution, well defined, and located in non-dependent areas. Approximately 50% of patients present with both urticaria and angioedema.[7] These patients generally have mast-cell mediated mechanisms for their symptoms. Patients with ACE-inhibitor angioedema, in contrast, present with isolated angioedema. In fact, up to 68% of cases of isolated angioedema are due to an ACE-inhibitor.[8, 9]

Studies examining the presenting signs and symptoms of patients with ACE-inhibitor angioedema are primarily limited to retrospective cohorts, case series and case reports. The most common signs are asymmetric swelling of the lips and face.[8, 10-14] Additional signs and symptoms reported in the literature include shortness of breath, swelling of the tongue, the floor of the mouth, neck, and eyelids. [8-15] Dysphagia, dysphonia, odynophagia, stridor, hoarseness, and drooling have also been reported.[8-15] In rare cases, involvement of the abdominal viscera can occur causing abdominal pain, nausea, and vomiting.[1, 3]

Recommendation: *ACE-inhibitor angioedema should be considered in any patient presenting with isolated, asymmetric swelling of the lips, tongue, floor of the mouth, face, eyelids, and neck.*

Level of Recommendation: B

Recommendation: Medications for the Treatment of ACE-inhibitor angioedema

Patients with allergic emergencies presenting to an emergency department often receive medications including epinephrine, anthistamines, and corticosteroids. Since ACE-inhibitor angioedema is not mediated by mast cell degranulation, the efficacy of these medications remains controversial.

There are no randomized, controlled, double-blind trials evaluating the efficacy of epinephrine, antihistamines, or corticosteroids in the treatment of patients with ACE-inhibitor angioedema. Studies reporting the use of these medications to treat ACE-inhibitor angioedema are limited to retrospective reviews, case series and case reports primarily from single centers. The percentage of patients receiving epinephrine, H_1 and H_2 antihistamines, and corticosteroids is variable across all studies evaluated in this literature review. It is not clear from the current literature whether patients improved as a result of these medications or

simply resolution of angioedema with cessation of the ACE-inhibitor. Kostis, et al reviewed over 12,000 patients treated with an ACE-inhibitor and found an incidence of angioedema of 0.68%.[10] Over 50% of patients with ACE-inhibitor angioedema received no medications with any intubations or death reported by the authors.[10] In general, ACE-inhibitor angioedema lasts 24 to 48 hours. Importantly, there have been no adverse events reported in the literature for patients who received any of these medications for ACE-inhibitor angioedema.

Recommendation: *There is currently insufficient evidence to recommend for or against the administration of epinephrine, antihistamines, or corticosteroids in the treatment of ACE-inhibitor angioedema..*

Level of Recommendation: Indeterminate

Recommendation: Role of Fiberoptic Examination (FOE) in ACE-inhibitor angioedema

Angioedema of the upper airway (larynx) can be a life-threatening condition. FOE provides the emergency physician the ability to evaluate the severity of laryngeal swelling. Laryngeal edema is considered an ominous finding indicative of severe disease and the need for admission to an intensive care unit (ICU).

There are no randomized, controlled trials evaluating the efficacy of FOE in the ED management of ACE-inhibitor angioedema. Studies on the use of FOE in patients with ACE-inhibitor angioedema are limited to retrospective reviews, case series and case reports primarily from single centers. This review of the literature demonstrates that patients reporting odynophagia, dyspnea, dysphonia, hoarseness, dysphagia, or those with respiratory distress, stridor, and drooling were more likely to have laryngeal edema.[8, 9, 11, 14-16] Patients with these symptoms should undergo FOE to determine the presence and extent of laryngeal involvement. Importantly, no patient with a normal larynx on FOE has progressed to require emergent intubation.[17]

Recommendation: *Patients presenting with signs or symptoms of laryngeal edema such as odynophagia, dyspnea, dysphonia, dysphagia, stridor, drooling, or respiratory distress should undergo FOE in the ED to determine the severity of laryngeal edema.*

Level of Recommendation: Indeterminate

Recommendation: Intubation and Admission Criteria in ACE-inhibitor Angioedema

Although a relatively rare occurrence, emergency physicians must be prepared to emergently secure the airway of patients with angioedema. Endotracheal intubation or cricothyroidotomy may be necessary to maintain airway patency and ventilation. As such, it is helpful to identify presenting signs or symptoms that predict the need for endotracheal intubation in patients with ACE-inhibitor

angioedema. The current literature on indications for intubation of the patient with ACE-inhibitor angioedema is limited to retrospective reviews primarily from single centers. These reviews indicate that patients presenting with respiratory distress, stridor, drooling, and edema of the floor of the mouth were more likely to require intubation.

For the patient who does not require immediate intubation, the emergency physician is often faced with the difficult decision of whether to admit the patient to the hospital or observe the patient in the ED. The literature on indications for admission in ACE-inhibitor angioedema is variable and primarily limited to retrospective reviews from single centers. Based upon this literature review, factors that identified the need for admission included a previous history of angioedema, tongue edema, pharyngeal edema (palate, uvula), laryngeal edema (true vocal cords, false vocal cords, arytenoids, aryepiglottic folds, epiglottis), and the lack of improvement during the ED course.[8, 9, 11, 12, 16]

The literature on ED observation of patients with angioedema is limited to retrospective reviews from single centers. Based upon this literature review, patients with angioedema of the face or lips may be observed in the ED for progression of symptoms.[8, 11, 14] There is currently no randomized, prospective, controlled trial evaluating the optimum observation period. Observation periods between 4 to 8 hours have been reported without adverse events.[17]

Recommendation: *Patients presenting with respiratory distress, stridor, and drooling should be immediately intubated. Also, intubation should be considered for the patient with edema of the floor of the mouth. Given the potential for airway compromise, patients with laryngeal edema on FOE should be admitted to the ICU. Patients who have pharyngeal edema, tongue edema, or those who fail to improve during the course of their ED stay should be admitted to a monitored bed. Patients with angioedema limited to the lips or face may be observed in the ED and, provided there is no progression of symptoms, discharged to home with discontinuation of the ACE-inhibitor.*

Level of Recommendation: B

7. List All Conflicts of Interest

There were no conflicts of interest were declared by the authors or committee reviewers.

8. Discussion

The literature review for this clinical guideline focused on the ED management of patients with angioedema secondary to an ACE-inhibitor. Important aspects of ED management include the administration of medications, identifying patients who require emergent intubation or cricothyroidotomy, performing fiberoptic

examination for laryngeal involvement, and determining which patients can be safely observed in the ED versus those who need admission to the hospital.

Importantly, the current literature on ACE-inhibitor angioedema is primarily limited to retrospective reviews, case series, and case reports from single institutions. There remains no prospective, controlled, double-blind, randomized study evaluating the utility of antihistamines, corticosteroids, FOE, and observation of ED patients with ACE-inhibitor angioedema. Therefore, the recommendations listed in this guideline are based upon the available evidence to date. Until additional studies of adequate methodology and power are published, emergency physicians should continue to incorporate clinical judgment with these recommendations when managing ED patients with ACE-inhibitor angioedema.

References:

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