Literature Review and Grading

What is the Emergency Department Management of Patients with Angioedema Secondary to an ACF-inhibitor? (11/12/2020) Undate to the 2011 CPC statement.

ACE-inhibitor? (11/12/2020) Update to the 2011 CPC statement.				
PUBLICATION	GRAD E	QUALITY	COMMENTS	
 Adebayo O, Wilkerson RG. Angiotensin-converting enzyme inhibitor-induced angioedema worsened with fresh frozen plasma. 	E	OUTSTANDING	Case report on FFP	
Am J Emerg Med. 2017 Jan;35(1):192.e1-192.e2. doi: 10.1016/j.ajem.2016.06.089. Epub 2016 Jun 28. No abstract available.				
 Akinduro OO, Patel V, Thomas T, Ahmad FU. Two cases of severe angio-oedema and rationale for their response to icatibant. 	Е	ADEQUATE	Case 1: ACEI-induced angioedema that responded to icatibant. Case 2: patient on ACEI but the authors called it idiopathic and icatibant did not help	
BMJ Case Rep. 2015 Dec 17;2015. pii: bcr2015213228. doi:10.1136/bcr-2015- 213228. No abstract available.				
3. Armengol G, Faisant C, Benhamou Y.	F	UNSATISFACTOR HY	Letter to the editor. No methodology	
Icatibant in ACE-inhibitor-induced angioedema.				
N Engl J Med. 2015 May 7;372(19):1867. doi: 10.1056/NEJMc1503671. No abstract available.				
4. Bartal C, Zeldetz V, Stavi V, Barski L.	E	OUTSTANDING	Case report of 76F. Treated with icatibant. Dyspnea relieved within minutes. Swelling almost	
The role of icatibant-the B2 bradykinin receptor antagonist-in life-threatening laryngeal angioedema in the ED.			disappeared after 30m	
Am J Emerg Med. 2015 Mar;33(3):479.e1-3. doi: 10.1016/j.ajem.2014.08.055. Epub 2014 Aug 27.				

		1	
5. BaÅŸ M, Greve J, Stelter K, Havel M, Strassen U, Rotter N, Veit J, Schossow B, Hapfelmeier A, Kehl V, Kojda G, Hoffmann TK. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. N Engl J Med. 2015 Jan 29;372(5):418-25. doi: 10.1056/NEJMoa1312524	А	Adequate	Industry-sponsored, multicenter, phase 2, double blind, double dummy design. 27 patients included in analysis. 8.0 hours vs 27.1 hours for median time to complete resolution
6. Bernstein JA, Moellman JJ, Collins SP, Hart KW, Lindsell CJ. Effectiveness of ecallantide in treating angiotensin-converting enzyme inhibitorinduced angioedema in the emergency department. Ann Allergy Asthma Immunol. 2015 Mar;114(3):245-9. doi:	А	Adequate	Industry- sponsored, 2- center, phase 2, triple blind design. 50 patients included in analysis. Discharge criteria met in < 4 hours in 31% of ecallantide
10.1016/j.anai.2014.12.007. Epub 2015 Jan 16.			patients and 21% of placebo
7. Bolton MR, Dooley-Hash SL.			οι μιαυσμυ
Angiotensin-converting enzyme inhibitor angioedema. J Emerg Med. 2012 Oct;43(4):e261-2. doi: 10.1016/j.jemermed.2011.03.029. Epub 2011 May 7. No abstract available.	Е	Poor	Case report of 76M. Treated with FFP. Nearly complete resolution over the next 2h
O Dovo M. Critlanta N. Cala Carilla			All potionts
8. Bova M, Guilarte M, Sala-Cunill A, Borrelli P, Rizzelli GM, Zanichelli A. Treatment of ACEI-related angioedema with icatibant: a case	D.	Adequate	All patients received standard of care treatment. After treatment with icatibant symptom relief
series.			was reported at 30 min (IQR 27.5-70
Intern Emerg Med. 2015 Apr;10(3):345-50. doi: 10.1007/s11739-015-1205-9.			min). Complete resolution of sx at 5h (IQR 4-7h). A comparison was
Epub 2015 Feb 10			made to to the 10

9. Chan NJ, Soliman AM. Angiotensin converting enzyme inhibitor-related angioedema: onset, presentation, and management. Ann Otol Rhinol Laryngol. 2015 Feb;124(2):89-96. doi: 10.1177/0003489414543069. Epub 2014 Jul 24.	D.	Outstanding	patients who had previously had angioedema where complete resoluation was at 54h (IQR 33-63h) Retrospective analysis of 88 patients. Looked at Onset and symptoms. Minimal discussion regarding treatment
10. Charmillon A, Deibener J, Kaminsky P, Louis G. Angioedema induced by angiotensin converting enzyme inhibitors, potentiated by m-TOR inhibitors: successful treatment with icatibant. Intensive Care Med. 2014 Jun;40(6):893-4. doi: 10.1007/s00134-014-3290-z. Epub 2014 Apr 16. No abstract available.	E.	Poor	65F on quinapril and everolimus for breast cancer. Regression of swelling 1 hour after administration of icatibant
11. Cheong E, Dodd L, Smith W, Kleinig T.			52M on perindipril who received alteplase. lcatibant

Icatibant as a Potential Treatment of Life-Threatening Alteplase-Induced			given. Upper airway edema
Angioedema.	E.	Poor	visibly improved within 15 min
J Stroke Cerebrovasc Dis. 2018			complete
Feb;27(2):e36-e37. doi:			resolution within 2 hours
10.1016/j.jstrokecerebrovasdis.2017.09.0			nouis
39. Epub 2017 Oct 31.			5
12. Curtis RM, Felder S, Borici-Mazi R,			Retrospective chart review of
Ball I. ACE-I Angioedema: Accurate Clinical			chart review of cases of AAE
Diagnosis May Prevent Epinephrine-			(includes ACEi
Induced Harm.	D.	Poor	and ARB induced
maded nam.	5.	1 001	angioedema) 2
West J Emerg Med. 2016 May;17(3):283-			patients who
9. doi:10.5811/westjem.2016.2.29224.			received
Epub 2016 Apr 26.			epinephrine had morbidity
13. Fok JS, Katelaris CH, Brown AF,			13 patients
Smith WB.			received icatibant.
Icatibant in angiotensin-converting			4 patients
enzyme (ACE) inhibitor-associated	D.	Good	intubated
angioedema.			
Late of Mark I 2045 A - 45(0) 024 7			
Intern Med J. 2015 Aug;45(8):821-7. doi: 10.1111/imj.12799.			
doi: 10.1111/1111J.12799.			
14. Gallitelli M, Alzetta M.			
leatibant: a novel approach to the			
Icatibant: a novel approach to the treatment of angioedema related to the			76M with 3
use of angiotensin-converting enzyme			previous
inhibitors.			presentations (4
			total). On 4th
Am J Emerg Med. 2012			presentation after getting icatibant
Oct;30(8):1664.e1-2. doi:			his swelling almost
10.1016/j.ajem.2011.09.014. Epub 2011	E.	Adequate	resolved
Nov 17.			completely by 10
45 Crave I Dec M Haffara TV			hours.
15. Greve J, Bas M, Hoffmann TK, Schuler PJ, Weller P, Kojda G,			Prospective case series of 10
Strassen U.			subjects
30,000011 01	I		,

Effect of C1-Esterase-inhibitor in angiotensin-converting enzyme inhibitor-induced angioedema. Laryngoscope. 2015 Jun;125(6):E198-202. doi: 10.1002/lary.25113. Epub 2015 Jan 13.	C.	Adequate	compared to historical cohort of 47 patients. Compared treatment with C1- INH concentrate. 10.1 hours vs 33.1h
16. Hahn J, Trainotti S, Hoffmann TK, Greve J. Drug-Induced Inhibition of Angiotensin Converting Enzyme and Dipeptidyl Peptidase 4 Results in Nearly Therapy Resistant Bradykinin Induced Angioedema: A Case Report. Am J Case Rep. 2017 May 25;18:576-579.	E.	Adequate	83F on ACEi and DPP-IV. Treated with C1-INH and icatibant with slow response
17. Hannoodi F, Sabbagh H. ACE Inhibitor-Induced Angioedema following Cervical Spine Surgery. Case Rep Cardiol. 2017;2017:4268962. doi: 10.1155/2017/4268962. Epub 2017 Mar 1.	E.	Good	54F on ACEi who was intubated for neck surgery. Unable to be extubated due to edema at the level of the arytenoids. Treated with dexamethasone for 4 days. After Acei stopped she was extubated the next day.
18. Hassen GW, Kalantari H, Parraga M, Chirurgi R, Meletiche C, Chan C, Ciarlo J, Gazi F, Lobaito C, Tadayon S, Yemane S, Velez C. Fresh frozen plasma for progressive and refractory angiotensin-converting enzyme inhibitor-induced angioedema. J Emerg Med. 2013 Apr;44(4):764-72. doi: 10.1016/j.jemermed.2012.07.055. Epub 2012 Oct 28. Review.	E.	Outstanding	7 cases of presumed ACEi-induced angioedema that all improved in temporal association to administration of FFP.

19. Howarth D. ACE inhibitor angioedema - a very late presentation. Aust Fam Physician. 2013 Dec;42(12):860-2.	E.	Good	77M intubated after failing steroids, antihistamines and epi
20. Illing EJ, Kelly S, Hobson JC, Charters S. Icatibant and ACE inhibitor angioedema. BMJ Case Rep. 2012 Aug 30;2012. pii: bcr2012006646. doi:10.1136/bcr-2012-006646.	E.	Adequate	62M with tongue swelling. Tx with hydrocortisone, chlorphenamine with no improvement. Given epi nebs and then a single dose of icatibant. Intubated. Extubated 48 hours later.
21. Jackeviciute J, Pilvinis V, Pilviniene R. Fatal outcome of late-onset angiotensin-converting enzyme inhibitor induced angioedema: A case report. Medicine (Baltimore). 2018 Aug;97(31):e11695. doi: 10.1097/MD.000000000011695.	E.	Adequate	89F intubated. Extubated. Reintubated with difficulty. ETT narrow due to edema. Cardiac arrest. ROSC. Blood clot at distal end of tube removed. FFP given with no improvement. Angioedema resolved 13 days later. Death at 24 days
22. Jacob J, Bardes I, Palom X, Carrizosa M, Fuentes E.			Letter to the editor about Fok article. 10 patients treated

Angiotensin-converting enzyme inhibitor-induced angioedema and icatibant: a new hope.	F.	Unsatisfactory	with icatibant who improved within 12 hours
Intern Med J. 2015 Oct;45(10):1093-4. doi: 10.1111/imj.12849. No abstract available.			
23. Javaud N, Achamlal J, Reuter PG, Lapostolle F, Lekouara A, Youssef M, Hamza L, Karami A, Adnet F, Fain O. Angioedema Related to Angiotensin-Converting Enzyme Inhibitors: Attack Severity, Treatment, and Hospital Admission in a Prospective Multicenter Study. Medicine (Baltimore). 2015 Nov;94(45):e1939. doi: 10.1097/MD.0000000000001939.	C.	Outstanding	prospective, multicenter, observational study in 4 French hospitals and call center. 62 patients enrolled. Symptom relief occurred significantly earlier in patients receiving specific treatment than in untreated patients (0.5 [0.5–1.0] versus 3.9 [2.5– 7.0] hours
24. Kaufman MB. ACE Inhibitor-Related Angioedema: Are Your Patients at Risk?	E.	Adequate	All 4 cases treated with standard therapy
P T. 2013 Mar;38(3):170-2.			
25. Korzeniowska K, Cielewiczi A, Pawlaczyk M, Motowidlo K, Andrys-Wawrzyniak I, Jablecka A. ANGIOEDEMA AFTER ANGIOTENSIN- CONVERTING ENZYME INHIBITORS. Acta Pol Pharm. 2017 May;74(3):983- 986.	E.	Adequate	2 cases. Treated with steroids and antihistamines
26. Krogh Nielsen T, Bygum A, Rye Rasmussen E.			60F. Neither adrenaline inhalations, intravenously

Life-threatening angio-oedema after the first dose of an ACE inhibitor-not an anaphylactic reaction. BMJ Case Rep. 2016 May 26;2016. pii: bcr2016214364. doi:10.1136/bcr-2016-214364.	E.	Adequate	administrated corticosteroids, atropine nor furosemide were effective and the patient soon become bradycardic. A tracheotomy was performed and the patient was placed on a ventilator.
27. Kuhlen JL Jr, Forcucci J. Angiotensin-converting enzyme inhibitor- induced unilateral tongue angioedema. Am J Med Sci. 2012 Nov;344(5):416-7. doi: 10.1097/MAJ.0b013e318258317f.	E.	Good	62M. Unilateral tongue angioedema. Improved then worsened. Tx with steroids and antihistamines. Intubated.
28. Leibfried M, Kovary A. C1 Esterase Inhibitor (Berinert) for ACE Inhibitor-Induced Angioedema: Two Case Reports. J Pharm Pract. 2017 Dec;30(6):668-671. doi: 10.1177/0897190016677427. Epub 2016 Nov 11.	E.	Adequate	2 cases of ACEi- Induced Angioedema. Treated with berinert. Case 1 treated with antihistamine, methylprednisolon e, epinephrine, and fresh frozen plasma. When symptoms did not resolve, intravenous C1 peptide esterase inhibitor (C1INH) was administered, with clinical improvement. Four hours later, symptoms returned and the patient underwent emergency

			tracheostomy. Case 2: received conventional treatment. Endo- tracheal tube placement was unsuccessful. While the patient was undergoing intubation in the operating room, intravenous C1INH was administered resulting in quick improvement of symptoms.
29. Leung E, Hanna MY, Tehami N, Francombe J. Isolated unilateral tongue oedema: the adverse effect of Angiotensin converting enzyme inhibitors.	E.	Adequate	Female with ACEi- angioedema. Tx with meds
Curr Drug Saf. 2012 Nov 1;7(5):382-3. 30. Lewis LM, Graffeo C, Crosley P, Klausner HA, Clark CL, Frank A, Miner J, larrobino R, Chyung Y. Ecallantide for the acute treatment of angiotensin-converting enzyme inhibitor- induced angioedema: a multicenter,	Α.	Outstanding	multicenter, phase 2, double-blind study with subjects randomized to receive a single subcutaneous dose of ecallantide
randomized, controlled trial. Ann Emerg Med. 2015 Feb;65(2):204-13. doi: 10.1016/j.annemergmed.2014.07.014. Epub 2014 Aug 30.			(10, 30, or 60 mg) or placebo plus physician-directed conventional therapy. discharge eligibility endpoint was met by 72% of the placebo group and 85%, 89%, and 89% of the ecallantide 10-, 30-, and 60-mg

	1	I	
			groups,
			respectively.
31. Lipski SM, Casimir G,			77F tongue
Vanlommel M, Jeanmaire			angioedema
M, Dolhen P.			administered 125
			mg of
Angiotensin-converting enzyme			methylprednisolon
inhibitors-induced angioedema treated	E.	Good	e and 0.5 mg of
by C1 esterase inhibitor concentrate			epinephrine
(Berinert®): about one case and review			subcutaneously.
of the therapeutic arsenal.			Fresh frozen
of the therapeutical serial.			plasma was
Cli - C D 2015 F-l- 2/2) 42C 20 -l-i			administered but
Clin Case Rep. 2015 Feb;3(2):126-30. doi:			there was no
10.1002/ccr3.171. Epub 2014 Dec 5.			improvement after
			4 h. Berinert four
			ampoules were
			injected (20
			Ul/Kg). In less
			than an hour, the
			swelling was
			absorbed and the
			patient remained
			in hospital for 48 h
			observation
32. Millot I, Plancade D,			67M on ACEi and
Hosotte M, Landy C,			DPP-4. 3rd
Nadaud J, Ragot C, Graffin			presentation for
B, Drouet C, Kanny G.			angiodema.
, , , ,			treated with
Treatment of a life-threatening laryngeal			epinephrine
bradykinin angio-oedema precipitated by	E.	Adequate	aerosols, i.v. dex-
dipeptidylpeptidase-4inhibitor and		/ lacquate	chlorpheniramine
angiotensin-I converting enzyme inhibitor			5 mg, and
			methylprednisolon
with prothrombin complex concentrates.			e 120 mg. The
D 14 11 2042 N 420/5\ 227 5 1 1			patient showed no
Br J Anaesth. 2012 Nov;109(5):827-9. doi:			improvement in
10.1093/bja/aes371. No abstract			the next hour.
available.			AVK antagonist,
			Kanokadw (LFB,
			France) 1500 IU,
			was adminis-
			tered. Dyspnoea
			and dysphonia
			regressed within

			20 min, and symptoms completely disappeared within 8 h. Further episodes treated with berinert and icatibant.
33. Okumu M, Ochola F, Bodo C, Apuoyo K, Odhiambo N, Ng'ong'a A. Enalapril-Induced Angioedema: Two Case Reports in a Rural Health Facility in Kenya. Cureus. 2018 May 2;10(5):e2572. doi: 10.7759/cureus.2572.	E.	Adequate	Case 1: 58F. Given IV dose of hydrocortisone and a 20 mg stat dose of intravenous chlorpheniramine were administered and the patient was observed for one hour. The edema was noted to subside Case 2: 55M. 4 mg intravenous dexamethasone injection and monitored for one hour. A gradual decrease in the swelling was observed about two hours after
34. Pucar PA, O'Sullivan M, Goudie A, Marr T, Brusch A. Successful treatment of ACE inhibitor- induced angioedema with icatibant, a bradykinin B2 receptor antagonist. Med J Aust. 2015 Jun 15;202(11):596-7. No abstract available.	E.	Adequate	65F. Treated with icatibant. On repeat FNE 10 minutes later, there was a significant improvement in her condition.

	1		
35. Rasmussen ER, Mey K, Bygum A. Isolated oedema of the uvula induced by intense snoring and ACE inhibitor. BMJ Case Rep. 2014 Aug 21;2014. pii: bcr2014205585. doi: 10.1136/bcr-2014-205585.	Е.	Adequate	50M. received complement C1-inhibitor concentrate ~15 units/kg injected intravenously over 10 min. Within about 40 min significant improvement of the oedema was observed and the patient's voice had normalised
36. Rasmussen ER, Bygum A. ACE-inhibitor induced angio-oedema treated with complement C1-inhibitor concentrate. BMJ Case Rep. 2013 Oct 4;2013. pii: bcr2013200652. doi:10.1136/bcr-2013-200652.	E.	Adequate	63M. He was treated with drugs for anaphylaxis (epinephrine, antihista- mine and corticosteroid), but the angio-oedema progressed and also began to involve the soft palate and uvula. 1000 units (11 units/kg) of Berinert (complement C1-inhibitor concentrate) had already been administered intravenously over 10 min and the angio-oedema had regressed significantly.

37. Raval P. A case report looking at ACE inhibitors as the cause of angioedema during dental treatment. Br Dent J. 2014 Jan;216(2):73-5. doi: 10.1038/sj.bdj.2014.2.	E.	Adequate	77M. Adrenaline and an antihistamine were administered to the patient
38. Shahani L. ACE inhibitor-induced intestinal angiooedema: rare adverse effect of a common drug. BMJ Case Rep. 2013 Jul 22;2013. pii: bcr2013200171. doi:10.1136/bcr-2013-200171.	E.	Adequate	50F. Hx of Crohns presenting with abdo pain. Lisinopril was discontinued and the patient was treated with antihistamines
39. Sinert R, Levy P, Bernstein JA, Body R, Sivilotti MLA, Moellman J, Schranz J, Baptista J, Kimura A, Nothaft W; CAMEO study group Randomized Trial of Icatibant for Angiotensin-Converting Enzyme Inhibitor-Induced Upper Airway Angioedema. J Allergy Clin Immunol Pract. 2017 Sep- Oct;5(5):1402-1409.e3. doi: 10.1016/j.jaip.2017.03.003. Epub 2017 May 25.	A.	Outstanding	phase III, 2- armed, randomized double-blind clinical trial was conducted at 59 centers severity of the ACE-leinduced angioedema attack was determined by the subject's worst severity rating at baseline among 4 clinical domains (difficulty breathing, difficulty swallowing, voice changes, and tongue swelling) Conventionally administered drugs, namely, antihistamines, corticosteroids, and epinephrine,

were allowed at any time before or after study drug administration. primary efficacy end point was time to meeting discharge criteria, defined as time from study drug administration to earliest time that difficulty breathing and difficulty swallowing were absent (rating of 0 out of 4), and voice change and tongue swelling were mild or absent (0 or 1). Between December 2013 and August 2015, 121 subjects with presumed ACEleinduced angioedema were randomized at 31 of 59 opened sites. no statistically significant differences between the 2 treatment groups in the primary efficacy end point of time to meeting discharge criteria (P 1/4 .63), the key secondary end point of TOSR (P 1/4 .57), or any other secondary end point

40. Stewart M, McGlone R. Fresh frozen plasma in the treatment of ACE inhibitor-induced angioedema. BMJ Case Rep. 2012 Aug 24;2012. pii: bcr2012006849. doi:10.1136/bcr-2012-006849.	E.	Good	2 cases of angioedema that temporally improved with administration of FFP
--	----	------	--

	_		4484 ()
41. Urnoski E, Grillo A,			41M. treated
Rosini JM.			initially with
Use of C1 Inhibitor for			diphenhydramine
Angiotensin-Converting Enzyme			25 mg i.v., meth-
(ACE) Inhibitor-Induced			ylprednisolone 125
Angioedema Decreases	E.	Good	mg i.v., and
Mechanical Ventilation Time.			ranitidine 50 mg i.v.
			His edema rapidly
J Emerg Med. 2015			progressed with left
Dec;49(6):e173-5. doi:			lip and further
10.1016/j.jemermed.2015.06.076.			tongue swelling. An airway alert was
Epub 2015 Sep 26.			called and nebu-
ļ ·			l lized lidocaine
			started for
			anticipated
			intubation. The pa-
			tient was ordered
			C1 inhibitor 1500
			units (17 mg/kg) i.v.
			Intubated prior to
			receiving C1-INH.
			Received C1-INH
			at approximately
			6:00 PM, the
			patient responded
			with marked
			decreased
			angioedema. The
			angioedema was

			noted to resolve
			symmetrically
42. Volans A, Ferguson R. Using a bradykinin blocker in ACE inhibitor-associated angioedema in the emergency department. BMJ Case Rep. 2013 Jan 31;2013. pii: bcr2012008295. doi: 10.1136/bcr-2012-008295.	E.	Good	

43. Wagner JG, Bench EM, Plantmason L. An Unusual Case of Angiotensin-Converting-Enzyme Inhibitor-Related Penile Angioedema with Evolution to the Oropharynx. West J Emerg Med. 2015 Dec;16(7):1185-7. doi: 10.5811/westjem.2015.8.28061. Epub 2015 Nov 18.	E.	Good	52M. Penile angioedema that progressed to involve oropharynx. given diphenhydramine 50mg IV, famotidine 40mg IV, and methylprednisolone 125mg IV for possible allergic reaction versus acute onset of angioedema. He was observed in the ED for six hours, without progression or significant improvement in symptoms, and discharged home
44. Nishad AAN, Arulmoly K, Priyankara SAS, Abeysundara PK. A Forgotten Cause of Allergy at ER That Is Still Difficult to Diagnose and Treat at Poor Resource Setting: Angioedema after Using Angiotensin Converting Enzyme Inhibitors for 4 Years. Case Reports Immunol. 2019 Jan 2;2019:1676391. doi: 10.1155/2019/1676391. eCollection 2019.	E.	Good	discharged home 68M treated with intramuscular Adrenaline 0.5 mg stat and intravenous hydrocortisone 200 mg. Discharged on prednisone.