Ace-Inhibitor Induced Angioedema: What You Probably Didn’t Learn in Paramedic Training

By Kristin Spencer, MS, NRP

If I were to ask you to list the treatment modality for angioedema, your list would probably include oxygen therapy, I.V., cardiac monitoring, pulse oximetry, capnography, IM epinephrine, corticosteroids, diphenhydramine and in some cases, rapid sequence intubation. In most cases of an allergy-induced angioedema, your answer would be spot-on. Angiotensin-converting enzyme inhibitor-related angioedema (ACEI-RA) is a different beast, however. Before I discuss why ACEI-RA is less than responsive to the standard pharmacological agents listed above, the epidemiology and pathophysiology of ACEI-RA will be covered.

More than 40 million people worldwide are prescribed ACE inhibitors, and chances are several of your previous patients have been taking them for heart failure or hypertension.\(^1\) ACE inhibitors are the drugs that end in the familiar “prils,” lisinopril, captopril, and enalapril, for example. Like any prescription medication, there are potential side effects from ACE inhibitors, angioedema being one of the most serious. Angioedema is estimated to occur in 0.1% to 0.7% of patients on ACE inhibitor therapy. Of those who present to the emergency department with angioedema, 35% of those are attributed to ACEI.\(^1\) Additionally, one study concluded that African-Americans are three times more likely to develop ACEI-RA within six months of starting ACE inhibitor therapy.\(^2\) The most common signs and symptoms of ACEI-RA are mild and may not even be reported by the patient; in other cases, the situation can be life-threatening. According to Almazroua, et. al (2013), the most common sign of ACEI-RA is asymmetric (and isolated) swelling of the lips and face, although cases of isolated swelling has been documented in the small bowel, genitals, uvula, tongue, and floor of the mouth. Urticaria is usually absent.\(^3\) Unlike other types of allergic reactions that can occur rapidly and aggressively, several studies have shown ACEI-RA can occur with those who have been taking ACE inhibitors for weeks, months—even years.\(^2\)

Most cases of angioedema is mediated by IgE antibodies—the endogenous antibodies that attack seemingly innocuous allergens (antigens) in those with Type I sensitivity reactions. Insect stings, seafood, pollen, and some medications are frequently associated with IgE-mediated allergic reactions. IgE antibodies have a high affinity for mast cells and basophils and when bonded together, results in the formation and subsequent release of chemical mediators. Of course, the chemical mediator closely examined in paramedic curriculum was, and is, histamine. Histamine causes its effects by binding to H1 and H2 receptors that cause contraction of smooth muscles of the airway and GI tract, increased vascular permeability, vasodilation, enhanced mucus production, pruritus, and gastric acid secretion. Translated, a histaminergic-mediated angioedema means your patient with allergy sensitivities could present with a runny nose, conjunctivitis, nausea and vomiting, diarrhea, bronchoconstriction, increased bronchial mucous secretions, generalized swelling, urticarial/ weals, and hypotension—a multi-systemic reaction.\(^1,3\) Again, angioedema induced by histamine will respond to conventional therapies like antihistamines and corticosteroids, pharmacological agents commonly emphasized in most paramedic curriculums. Interestingly, ACEI-RA is not IgE mediated; the physiology of the condition is caused by the levels of the blood vessel-dilating bradykinin in the body, a peptide. Bradykinin counterbalances the vasoconstrictive workings of the renin-angiotensin-aldosterone system, and is thought to be a primary mediator in non-allergic angioedemas.

There are two kinds of bradykinin receptors: B1 and B2. When bradykinin binds with these receptors, increased vascular permeability and isolated, non-pitting edema occurs. Glossitis is frequently seen.\(^5,6\) Given the pathophysiology behind ACEI-RA, you can now understand why conventional interventions for angioedema probably will not work with these specific cases.\(^1,2\) So, what do you do? Do
you not treat the angioedema? Of course you do. Most cases of angioedema are not caused by ACE inhibitors and, it may be difficult to make a precise correlation between the two. However, if you're a person who would prefer a specific treatment algorithm for ACEI-RA or a definitive diagnostic test, you will be sorely disappointed.

When assessing a patient with upper airway obstruction/edema, conduct a fastidious, yet rapid exam—early identification regarding its etiology is extremely time-sensitive, especially when dealing with ACEI-RA. For purposes of this discussion, the upper airway is defined as the conduit from the nose and mouth to the larynx.

You've probably heard the mantra to avoid the perils and pitfalls of approaching your patient with tunnel vision, and this bears repeating. Not all cases of angioedema are secondary to shellfish, hymenoptera stings or penicillin, so keeping a broad list of differentials is important. You must consider the likely causes of upper airway obstructions considering age, medical history, recent events, and physical examination. For example, you would not diagnose a young patient with a history of fever, dysphagia, sore throat, and drooling as ACEI-RA.

There are multiple causations for upper airway swelling—some are progressive and potentially lethal, while some more benign. Through your physical examination and history-taking, you can rule out some of the more common differentials:

- Burns
- Epiglottitis
- Laryngotracheobronchitis (croup)
- Massive maxillofacial trauma
- Acute laryngeal injury
- Ludwig’s Angina
- Laryngeal stenosis
- Laryngeal tumors

Understanding the underlying cause of common upper airway obstructions and identifying life threats is paramount, as treatment modalities differ. You would not treat a patient with massive maxillofacial injuries as you would a patient presenting with anaphylaxis, epiglottitis, or croup. Although the end point may be the same in most airway management challenges (e.g., oral intubation), patients with ACEI-RA may be non-intubatable through the oral cavity; glossitis may be severe enough to make the mouth impenetrable with an OPA, endotracheal tube, LMA®, Combitube®, or King Airway®. (As a side note, although glossitis may look outlandish, the larynx may not be affected and the patient can still move air.) If the patient needs ventilatory assistance, perform BVM ventilations while simultaneously watching the rise and fall of your patient’s chest to ensure adequate tidal volume. Observe SpO2, the patient’s color, mental status, heart rate, and ETCO2—your patient may respond surprisingly well. It would be difficult to justify performing, say, a surgical airway when assisted ventilations prove beneficial. Sometimes the least invasive practices are preferred over invasive procedures that may have catastrophic consequences.

If you determine BVM ventilations are ineffectual, intubate through the orotracheal route. If you cannot insert an ETT through the orotracheal route, consider the nasotracheal route. Although becoming a lost art and at times forgotten as a viable option, a scenario may arise when using the nasotracheal route may be your only option in securing a definitive airway.

Arguably controversial and not instituted in some regions and states, rapid sequence induction (RSI) is an option and should be included in every paramedic’s treatment toolbox. If necessary and viable, RSI can be very beneficial in cases of ACEI-RA when you have a conscious patient showing signs of imminent airway closure (e.g., stridor, hoarse voice, reports of dysphagia) or respiratory failure. If you anticipate a difficult intubation due to anatomic changes, prepare two or three different sizes of ETTs. If the larynx is edematous, you may not successfully pass a tube normally appropriate for the stature of your patient. If you are able to visualize the glottic opening, but are unsuccessful with direct laryngoscopy, consider using fiberoptic intubation if available.

In extreme cases, a cricothyroidotomy may be required when all other attempts have failed. According to Yatako and Mehta (2008), orotracheal intubation is successful in 97% of airway management cases, leaving only 3% of patients requiring immediate cricothyroidotomy. Don’t let these numbers lure you into thinking “I will never get that patient.” You may get “that” patient, and should always be prepared to perform this procedure if the worst case scenario falls in your lap. Practice surgical airways frequently.

Once you have determined, through ruling out various differentials, that ACEI-RI is the probable etiology for your patient’s angioedema, examine the airway and act accordingly based on the patient’s presentation. Your ultimate treatment goal is more than managing the airway through basic or advanced airway devices; attempts to abate airway swelling through
pharmacological agents is also vital.

Case studies show great promise in treating ACEI patients with fresh frozen plasma (FFP, Class II) or bradykinin blockers (e.g., icatibant, Class II). However, neither is carried in ambulances. Nor is there a precise antidote to treat ACEI-RA. Based on that harsh reality, paramedics are forced to rely on conventional therapies including epinephrine, corticosteroids, and antihistamines. According to some clinicians, evidence-based treatment recommendations for ACEI-RA are:

- Supplemental oxygen
- Securing the airway, assist ventilations if needed
- Pharmacologically-assisted intubation (RSI)
- Nasotracheal intubation if orotracheal intubation impossible
- Capnography, pulse oximetry
- I.V. and fluids, if necessary
- Although controversial, treatment still involves the consideration of H1 and H2 blockers (e.g., ranitidine, cimetidine/class indeterminate)
- Corticosteroids (e.g., prednisone, methylprednisolone/class indeterminate)
- Cardiac monitoring
- Racemic Epinephrine
- Epinephrine 1:1,000, 0.3-0.5 IM, repeat if needed

Examine the list above, you may question why histaminic antagonists and epinephrine are included as part of the suggested treatment plan for ACEI-RA given histamine release is not the triggering agent. Epinephrine is administered primarily for its alpha one properties; the vasoconstrictive actions may reduce swelling in the affected areas, although several case studies have shown less than impressive results when using epinephrine for bradykinin-mediated angioedema. Histamine blockers are generally used if the source of the angioedema is either histaminic-induced or unknown. It is reasonable to administer H1 and H2 blockers for angioedemas of unknown etiology, because there are relatively few, benign side effects. It is important to note that in a small study published in the New England Journal of Medicine (2013), Bass et al. found that patients with ACE-inhibitor-induced angioedema recovered nearly three times faster with the administration of a bradykinin blocker than those given a standard glucocorticoid/antihistamine treatment.

Although ACEI-RA is rarely examined in either initial or ongoing paramedical training, airway management is. If your patient shows signs of airway closure or indicators that airway compromise is imminent, be aggressive in securing the airway before it becomes impossible. Although basic maneuvers such as the insertion of an NPA and BVM ventilations may prove successful, watch your patient closely to determine how he/she is trending. Complete airway obstruction secondary to laryngeal edema may occur rapidly and unexpectedly. Immediate intubation, either the oral or nasal route, RSI, or in extreme cases cricothyrotomy, may be required. With those suspected of ACEI-RA this fundamental training may very well be the most important intervention we can make for these patients—after all, it always comes down to your ABCs.

About the Author

Kristin Spencer, MS, NRP, has been in EMS since 1994. She holds a B.S. in Criminal Justice from Old Dominion University and a B.S. in Journalism from OSU-Tulsa. She earned her Master's in Criminal Justice with honors from Missouri Southern State University (MSSU) in 2011. Kristin has been the EMS Director for Crowder College since 2005. In 2011, she was selected as Crowder's Outstanding Instructor. She is the Missouri State Coordinator for Advanced Medical Life Support, has published articles in JEMS, and is a Missouri POST certified instructor. She also teaches classes and seminars in Criminal Justice at MSSU.

References

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