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EMERGENCY DEPARTMENT MANAGEMENT OF PATIENTS WITH ACE-INHIBITOR ANGIOEDEMA

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☐ **Abstract—Background: Angiotensin-converting-enzyme inhibitors (ACEI) are one of the most prescribed medications worldwide. Angioedema is a well-recognized adverse effect of this class of medications, with a reported incidence of ACEI angioedema of up to 1.0%. Of importance to note, ACEI angioedema is a class effect and is not dose dependent. The primary goal of this literature search was to determine the appropriate Emergency Department management of patients with ACEI angioedema. Methods: A MEDLINE literature search from January 1990 to August 2012 and limited to human studies written in English for articles with keywords of ACEI angioedema. Guideline statements and non-systematic reviews were excluded. Studies identified then underwent a structured review from which results could be evaluated. Results: Five hundred sixty-two papers on ACEI angioedema were screened and 27 appropriate articles were rigorously reviewed in detail and recommendations given. Conclusion: The literature search did not support any specific treatment protocol with a high level of evidence due to the limited—and limitations of the—available studies.** © **2013 Elsevier Inc.**

☐ **Keywords—angioedema; angiotensin-converting-enzyme inhibitors; ACE inhibitors**

INTRODUCTION

Angiotensin-converting enzyme (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, with a reported incidence of ACE inhibitor (ACEI) angioedema ranging from 0.1% to 1.0% (3). ACEI angioedema is a class effect and is not dose dependent, and thus, symptoms can occur any time from a few hours up to 10 years after the initial dose (1). In fact, up to 40% of patients with ACEI angioedema present months to years after their initial dose (3).

The pathophysiology of ACEI angioedema remains controversial. Decreased degradation of bradykinin, a potent vasodilator that increases vascular permeability, is thought to be the primary pathophysiologic process for ACEI-induced angioedema. C1-inhibitor abnormalities, carboxyalkyl dipeptide N, urinary kallikrein, and inflammatory mediators such as interleukin-1 and tumor necrosis factor have also been proposed as mediators for ACEI angioedema (3,4).

This article seeks to review the medical literature on the topic of treatment for ACEI angioedema and to offer evidence-based recommendations to emergency physicians for evaluation and treatment of patients who present with this diagnosis. This work was done at the request of, and published as a clinical practice statement by, the American Academy of Emergency Medicine Clinical Guidelines Committee.

METHODS

A structured review of the medical literature using PubMed was performed and limited to studies published

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Table 1. The Definitions of the Grades of Evidence of the Articles

Grade A	Randomized clinical trials 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
Grade F	Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

from January 1990 to August 2012. Inclusion criteria were all studies involving human subjects and written in the English language and containing the keywords: angioedema and ACE inhibitors. The abstracts of the articles found in this search were assessed independently by two emergency physicians, to determine which articles should be pulled for more detailed review based on their suspected relevance to the clinical question. Studies included for the final detailed review were limited to randomized controlled trials, prospective trials, retrospective cohort trials, case series, and case reports in human subjects. General review articles were not included for formal review. Each of the articles selected underwent a Grade of Evidence Review. Each of the selected articles was subjected to detailed review by at least two of the authors. The level of the evidence was assigned a grade using the definitions as noted in Table 1 and were based on reference focus, specific research design, and methodology.

Each of the selected articles was also subjected to detailed review and assigned a Quality Ranking based on a critical assessment with regards to quality of the design and methodology. This includes Design Consideration (focus, model structure, presence of controls, etc.) and Methodology Consideration (actual methodology utilized). The definitions of the Quality Ranking scores are included in Table 2.

Independent review of the articles as well as discussion and joint review by the authors was undertaken to answer the clinical question. The references were sorted into three 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.

Finally, recommendations were made based on the review of the literature and assigned a level of recommendation, which is defined in Table 3 (5–31).

RESULTS

The search parameters for the term ACE inhibitors angioedema resulted in 562 unique articles of human studies and written in English. The abstracts of the 562 articles were assessed independently by two physicians, and a combined total of 27 articles were deemed appropriate to be pulled for additional screening. These articles include: randomized controlled trials (n = 2), prospective cohort studies (n = 1), retrospective cohort studies (n = 13), case series studies (n = 5), and case reports (n = 6). A summary of the articles is located in Table 4 (5–31).

The primary goal of this literature search was to determine the appropriate Emergency Department (ED) management of patients with ACEI 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 ACEI Angioedema

Angioedema is characterized by the abrupt onset of nonpitting, non-pruritic swelling that involves the reticular dermis, subcutaneous, and submucosal layers (1,32,33). Lesions are typically asymmetric in distribution, well defined, and located in non-dependent areas. Approximately 50% of patients present with both urticaria and angioedema (34). These patients generally have mast-cell-mediated mechanisms for their symptoms. Patients with ACEI angioedema, in contrast, present with isolated

Table 2. The Definitions of the Quality-Ranking Scores of the Articles

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