

# THE USE OF EPINEPHRINE FOR OUT-OF-HOSPITAL TREATMENT OF ANAPHYLAXIS: RESOURCE DOCUMENT FOR THE NATIONAL ASSOCIATION OF EMS PHYSICIANS POSITION STATEMENT

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## ABSTRACT

Anaphylaxis is a potentially life-threatening condition that requires both prompt recognition and treatment with epinephrine. All levels of emergency medical services (EMS) providers, with appropriate physician oversight, should be able to carry and properly administer epinephrine safely when caring for patients with anaphylaxis. EMS systems and EMS medical directors should develop a mechanism to review the charts of patients who received epinephrine and were not in cardiac arrest. This will help to ensure the safe and appropriate use of epinephrine in order to provide continued quality improvement. Despite the safety of epinephrine, EMS systems that carry epinephrine autoinjectors should establish protocols to deal with patients or emergency responders who have an unintentional injection of epinephrine into the hand or digit. Continued research is needed to better define the role that EMS plays in the management of anaphylaxis. This paper serves as a resource document to the National Association of EMS Physician position on the use of epinephrine for the out-of-hospital treatment of anaphylaxis. **Key words:** EMS; prehospital; anaphylaxis; epinephrine; intramuscular epinephrine

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## INTRODUCTION

Anaphylaxis is a sudden-onset, systemic allergic reaction that can cause rapid death if not immediately identified and appropriately treated. The universal

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standard for the treatment of anaphylaxis is administration of epinephrine. Unfortunately, anaphylaxis is frequently both underrecognized and undertreated by clinicians.<sup>1-6</sup> The exact incidence and prevalence of anaphylaxis are difficult to determine secondary to the lack of specific, universally accepted diagnostic criteria, as well as underrecognition by medical personnel. However, anaphylaxis has been reported to occur with a frequency ranging from 30 to 2,000 episodes per 100,000 persons, with a prevalence as high as 2% over a lifetime.<sup>4,7</sup> There is only one study documenting the prehospital incidence of anaphylaxis. It revealed that 0.4% to 0.9% of emergency medical services (EMS) runs in a population of 13 million were for allergic reactions.<sup>8</sup> Death is uncommon, with one article citing an estimate of 150 to 200 deaths per year from food anaphylaxis alone.<sup>9</sup> Again, reliable mortality statistics for anaphylaxis are challenging to quantify, because of the degree of underrecognition and lack of uniformity in diagnostic criteria.

Because prospective, randomized clinical trials on anaphylaxis in the out-of-hospital environment are lacking, recommendations for prehospital treatment of anaphylaxis, like many EMS best practices, must be extrapolated from expert consensus, and from data obtained in settings other than the out-of-hospital arena. This paper discusses the importance of timely administration of epinephrine by EMS, the rationale for allowing all levels of EMS providers to carry and administer epinephrine to those with anaphylaxis, and the evidence supporting the use of intramuscular (IM) epinephrine over other routes. In addition, this document is the resource document to the National Association of EMS Physicians (NAEMSP) position statement on the use of epinephrine for out-of-hospital treatment of anaphylaxis.<sup>10</sup>

## IMPORTANCE OF EARLY ADMINISTRATION OF EPINEPHRINE IN THE TREATMENT OF ANAPHYLAXIS

Epinephrine is widely accepted as the initial treatment of choice for patients experiencing anaphylaxis.<sup>5,11-16</sup> Because most cases of anaphylaxis occur in the out-of-hospital environment, it is imperative that EMS providers have the capability to administer epinephrine in a timely fashion.<sup>5,7,11,17</sup> Delayed

administration of epinephrine is associated with increased morbidity and mortality,<sup>13,15,17–19</sup> underscoring the importance for prehospital personnel to initiate treatment with epinephrine to patients presenting with anaphylaxis. Epinephrine is the cornerstone of treatment for anaphylaxis from all causes, so emphasis should be placed on epinephrine administration, and epinephrine should be given priority over all other adjunctive medications, such as antihistamines, corticosteroids, and intravenous (IV) fluids.

### RATIONALE FOR ALLOWING BASIC LIFE SUPPORT PROVIDERS TO CARRY AND ADMINISTER EPINEPHRINE

Much of the nation's rural EMS systems rely heavily on basic life support (BLS) providers for their care and transport. Given that anaphylaxis is a true medical emergency that occurs most commonly in the out-of-hospital environment, that it requires timely administration of epinephrine in order to reduce morbidity and mortality, that epinephrine has a wide safety profile, and that unintentional injection of epinephrine by epinephrine autoinjectors (EAI) apparently does not cause harm, it seems reasonable to allow BLS providers to carry epinephrine in the form of an EAI for the treatment of patients with anaphylaxis.

Currently, emergency medical technicians (EMTs; formerly referred to as EMT-Basics) receive two hours of training on allergic reactions and anaphylaxis in the U.S. Department of Transportation (DOT) National Standard Curriculum.<sup>20</sup> Emergency medical technicians are also taught how to administer EAIs in cases of anaphylaxis. The important role that EMTs play in the out-of-hospital care of patients with this potentially life-threatening condition is appropriately summarized in the DOT's curriculum by the following statement, "The ability to recognize and manage a severe allergic reaction (anaphylaxis) is possibly the only thing standing between a patient and imminent death."<sup>20</sup> It is already allowable for EMTs to assist in the administration of a patient's own, physician-prescribed, EAI in cases of anaphylaxis.

While emergency medical responders (EMRs; formerly referred to as first responders) do not receive formal training in the recognition or treatment of anaphylaxis at this time, they do receive training in the use of autoinjectors for self- or peer administration of lifesaving medications in the event of hazardous materials incidents.<sup>21</sup> Further, the National EMS Scope of Practice Model defines the scope of practice for EMRs to include simple skills for lifesaving interventions of critically ill patients.<sup>21</sup> Certainly, the administration of EAIs for life-threatening anaphylaxis qualifies as being within the goals of the scope of practice for EMRs.

Therefore, despite the deficiency of published literature regarding anaphylaxis in EMS, the NAEMSP believes that EMRs should be allowed to both carry and administer EAIs to patients with anaphylaxis. This would require physician oversight, additional training in the recognition and management of anaphylaxis, and quality assurance (QA) programs. There are several valid reasons as well as some evidence to support allowing BLS providers to carry EAIs.

### Evidence Supporting the Safe Use of Epinephrine by Basic Life Support Providers for the Treatment of Anaphylaxis

To date there have been three studies evaluating BLS providers' ability to recognize and safely treat anaphylaxis with epinephrine.

Fortenberry et al. described a case series of EMTs' administration of epinephrine using preloaded syringes for the treatment of eight patients experiencing anaphylaxis from *Hymenoptera* stings in a wilderness setting. No major adverse events occurred in this setting. The authors concluded that the use of epinephrine by EMT-Basics in a rural/wilderness environment is safe with appropriate physician supervision.<sup>11</sup>

Rea et al. used a case-control design to assess whether firefighters/EMTs could both appropriately recognize anaphylaxis and safely treat patients with epinephrine using an EAI. The EMTs' decisions to treat with epinephrine agreed with physician review in 86% of cases and, again, there were no major adverse outcomes in any of the 22 patients treated by EMTs using an EAI. Further investigation by the researchers on cases where there was disagreement between EMT and physician reviewer found that medical control had ordered the EMT to administer the epinephrine in one case, and paramedics had given a second dose for persistent symptoms. If medical control and paramedic agreement are taken into account, then it can be concluded that EAIs were given appropriately by the EMTs in 21 of 22 patients, or 95% of the time. The authors concluded that EMTs can use epinephrine in a discriminating and safe manner for patients with presumed anaphylaxis.<sup>22</sup>

Lindbeck et al. described the implementation of an out-of-hospital provider program for the recognition and treatment of anaphylaxis by both advanced life support (ALS) and BLS providers. Epinephrine was administered by BLS personnel in the out-of-hospital environment, after completion of a two-hour course on allergic reactions. Fourteen patients experiencing anaphylaxis were treated, with no adverse events recorded.<sup>23</sup>

While the above studies clearly lack significant numbers, and none were prospective, they all were conducted in the out-of-hospital environment,

epinephrine was administered by BLS providers in all three studies, and no adverse events were recorded in any of the studies.

There may also be concern for the unintentional injection of epinephrine into the digits or hands of both EMS providers and patients while handling EAs. Three studies have done extensive systematic reviews and none found any documented cases of necrosis or short- or long-term sequelae after unintentional injection of high-dose epinephrine into the hand or digits. Most cases required no treatment at all, while others were successfully treated with injections of terbutaline or phentolamine and/or application of nitroglycerin paste (nitro paste).<sup>24–26</sup> This underscores the need for a policy outlining the necessary procedures to treat an unintentional injection. However, should an unintentional injury occur, it appears to be readily treatable.

### Safety Profile of Epinephrine

One issue of concern is the safety of epinephrine administration in general. Many health care providers are hesitant to provide epinephrine to anaphylaxis patients out of concern for potential adverse effects, even though there are no absolute contraindications to the use of epinephrine for anaphylaxis.<sup>2,5,14,16,27</sup> There are indeed case reports of fatal cardiac arrhythmias and acute myocardial infarctions, among other cardiovascular and neurologic complications, in patients who received epinephrine during anaphylaxis.<sup>17</sup> However, these cases tend to occur in older patients with pre-existing cardiovascular disease. Elderly patients are also more likely to be taking prescription beta-blockers and/or angiotensin-converting enzyme (ACE) inhibitors, which independently have been shown to make anaphylaxis more severe and refractory to typical treatments.<sup>5,28</sup> Another principal issue regarding the rare fatal reactions to epinephrine is that they most often occur with the use of IV bolus dosing and/or administration at inappropriately high doses.<sup>28–30</sup>

There is some controversy over fatalities deemed to be from epinephrine when used to treat anaphylaxis. It is likely that the reason these patients were receiving IV epinephrine is because they were refractory to the more commonly used initial subcutaneous (SQ) or IM route and were generally sicker. Other authors/researchers make the claim that anaphylaxis may specifically target the myocardium and that lethal arrhythmias, elevated cardiac biomarkers, and ischemic changes on electrocardiograms may be caused by the anaphylaxis itself. All of the previously stated adverse events have been documented in patients with anaphylaxis who did not receive epinephrine.<sup>31–33</sup> The ability to dissect the role that epinephrine plays in fatal anaphylaxis away from the known effects of anaphylaxis is difficult at best. It is

important to remember that these are generally case reportable incidents, and epinephrine has generally been deemed safe for administration for the treatment of anaphylaxis, especially the SQ/IM route.

In general, epinephrine enjoys an impressive safety profile, even when given via the IV route, as demonstrated by studies that have shown IV administration of epinephrine to be safe in patients with severe asthma.<sup>34,35</sup> The NAEMSP is not recommending IV use of epinephrine by BLS providers, but merely that these providers have the ability to both carry and administer EAs at fixed doses via the IM route.

### Political Climate Surrounding the Use of Epinephrine for Anaphylaxis

Many states have enacted legislation to allow more liberal use of EAs by BLS providers, and it is championed by the Food Allergy & Anaphylaxis Network (FAAN).<sup>36</sup> A recent study in 2009 by Wallace et al. surveyed EMS medical directors in all 50 states to ascertain the availability of epinephrine for anaphylaxis in the field and the type of provider that is allowed to administer and/or carry epinephrine. All 50 states allow paramedics to administer epinephrine and, interestingly, 17 states require that epinephrine be carried by EMT responders.<sup>37</sup>

Legislation recently passed in Alaska allowing public-sector employees (e.g., camp counselors, scout leaders, tour guides, and schoolteachers) to administer epinephrine to individuals experiencing anaphylaxis.<sup>38</sup> In 2010, the New York State legislature passed a bill that will mandate all ambulances in the state of New York, regardless of the level of responder, to carry epinephrine for the treatment of anaphylaxis.<sup>39</sup>

### Other Reasons to Support the Use of Epinephrine by Basic Life Support Providers

Studies have shown that, unfortunately, people for whom EAs are prescribed for anaphylaxis often do not carry them at all times. Sicherer et al. interviewed 101 families for whom EAs were prescribed for previous anaphylaxis, and found that only 55% of the families had unexpired and on-hand EAs at the time of the interview.<sup>40</sup> Other studies have demonstrated similar patterns, with patients carrying EAs 47% to 75% of the time.<sup>42,42</sup> Patients were often unaware of expiration dates as well.<sup>41</sup> In addition, one study showed that only 48% of parents were able to state more than one usual symptom for which epinephrine should be given to their child.<sup>43</sup> There may also be a need for multiple doses of epinephrine in refractory cases of anaphylaxis.

## EVIDENCE SUPPORTING THE INTRAMUSCULAR ROUTE OF ADMINISTRATION FOR ANAPHYLAXIS

Historically, the treatment of choice for anaphylaxis has been SQ injection of epinephrine, often in the deltoid/upper arm region. However, several studies, coupled with consensus opinion of experts in the field of allergy and immunology, have concluded that epinephrine should initially be administered via the IM route, in the lateral thigh when possible. Simons et al. demonstrated in pediatric patients that the absorption of epinephrine given IM in the lateral thigh achieved higher plasma concentrations of epinephrine significantly sooner (average of 8 minutes versus 34 minutes) when compared with SQ injection in the thigh.<sup>44</sup> These findings were replicated in an adult population in a similar study by Simons et al. that compared the IM injection of epinephrine in the lateral thigh with injection of epinephrine via the SQ route in the thigh and deltoid region.<sup>45</sup> Both studies found that absorption of epinephrine was superior when given via the IM route in the lateral thigh compared with absorption of epinephrine given via the SQ route in the deltoid or thigh region. The limitations in these two studies were that the patients were not experiencing anaphylaxis at the time; however, as discussed later in this article, there are tremendous challenges to studying anaphylaxis prospectively.

Again, relying on expert consensus in the international community is important, as there are no out-of-hospital data looking at the comparison of these two routes of administration. The following organizations are currently recommending the use of IM epinephrine for the first-line treatment of anaphylaxis: American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,<sup>46</sup> New Zealand Resuscitation Council Guidelines,<sup>2</sup> Resuscitation Council of the United Kingdom,<sup>47</sup> World Allergy Organization,<sup>5</sup> and the National Institute of Allergy and Infectious Diseases (NIAID)/FAAN.<sup>48</sup> Additionally, a review by the Cochrane Collaboration<sup>14</sup> recommended that the initial emergency treatment of choice when treating anaphylaxis is IM epinephrine.

There has been some concern over the ability of the EAI needle to perfectly administer epinephrine into the muscle because of differences in individual body habitus and fat distribution as well as increasing obesity in the population. In the case of morbid obesity or concerns that the EAI will not be able to reach muscle, it would obviously still be acceptable to give epinephrine using an EAI, even if there were a concern that the epinephrine might be deposited subcutaneously, because of the lack of a better option.<sup>17,49</sup>

## NEED FOR QUALITY ASSURANCE, MEDICAL OVERSIGHT, AND CONTINUING EDUCATION

It is essential to have a QA program with physician-level involvement at each EMS agency that allows the use of epinephrine to treat anaphylaxis. Examples of this would be to generate a review of each call that involves giving epinephrine to patients with a pulse (i.e., those who were not in cardiac arrest), to determine whether the patient received the appropriate dose of epinephrine as well as by the appropriate route for the given condition. It is also useful to have a mechanism in place to determine whether any adverse events occurred as a result of the administration of epinephrine. These types of QA programs can also serve as a way to identify any system problems and be able to address those issues through the education of field crews.

Currently, the DOT Curriculum for EMTs includes two hours of didactic time in instruction on allergic reactions. This includes utilizing training manikins to ensure proper use of EAIs. Regular in-servicing on this skill is important, as is increasing training and awareness about how to recognize anaphylaxis. For example, there is no mention of gastrointestinal (GI) symptoms in the current curriculum, and some studies have shown that GI symptoms such as nausea, vomiting, diarrhea, and abdominal cramping portend worse prognosis and are present in up to 40% of patients with anaphylaxis.<sup>14</sup> Emergency medical responders also have no formal training in anaphylaxis at this time. This is an opportunity for the EMS medical director and EMS agency to expand educational opportunities above and beyond current curricula.

The timely administration of epinephrine to patients with anaphylaxis should not be delayed in order to make real-time contact with online medical control. It is appropriate to allow providers at all levels to function on written standing orders to provide life-saving treatment with epinephrine to patients with anaphylaxis. However, the EMS system should have a mechanism in place to allow for physician contact that can provide oversight for field crews administering epinephrine to patients with anaphylaxis, specifically in regard to repeat dosing of epinephrine, for patients who are either pediatric or elderly, and for those with other comorbidities such as hypertension or coronary artery disease. If a patient does not respond to the first dose of epinephrine, it is appropriate to allow for an additional dose in 5 to 20 minutes. It is generally accepted that there are no absolute contraindications to the administration of epinephrine in anaphylaxis, and, when in doubt, providers should administer the initial dose of epinephrine. However, since epinephrine is generally not redosed for at least 5 minutes, this should allow ample time after the initial dose for the EMS provider to contact medical control

for further guidance regarding both the timing and the route of administration (e.g., IV administration) of any subsequent doses.

## CHALLENGES TO THE STUDY OF ANAPHYLAXIS

There are many hurdles to performing prospective trials on anaphylaxis in the emergency setting. There is no universally accepted definition for anaphylaxis, it is underrecognized by health care providers, and consent is difficult to obtain in a critically ill patient population. The latter necessitates adherence to the Food and Drug Administration's (FDA's) exception from informed consent for emergency research policies, which involves community notification as well as consultation; undertaking community consultation requires tremendous time, effort, and monetary resources to succeed.<sup>50</sup> It is also unethical to withhold treatment with epinephrine. There is no information on the pharmacokinetics and pharmacodynamics of epinephrine when given to humans with anaphylaxis, and it is difficult to compare severity of anaphylaxis, since it can vary widely between individuals.<sup>14</sup> One patient may present with hypotension and only GI symptoms, while another may have upper airway issues. Also, anaphylaxis occurs predominantly outside of the controlled, in-hospital environment and is almost always an unexpected event, making it even harder to obtain baseline information.

Nonetheless, it is important to continue attempts to better evaluate prospectively the effects of epinephrine on anaphylaxis in the prehospital arena, as well as to compare various routes of administration and dosing regimens. It is also necessary to continue to use surveillance data to discover any safety issues, and to study the effect that education has on the awareness and recognition of anaphylaxis by prehospital personnel.

## FUTURE DIRECTIONS

Sublingual disintegrating tablets of epinephrine have been studied prospectively in an animal model, resulting in peak plasma levels of epinephrine comparable to those achieved after IM injection.<sup>51</sup> If this proves to be useful as a treatment for anaphylaxis, it may be a helpful alternative for caregivers and patients who are reluctant to inject epinephrine via EAI. Other researchers are attempting to determine the efficacy and safety of IV epinephrine as a first-line treatment as well as intradermal epinephrine for milder reactions.<sup>52</sup> Some have proposed the use of epinephrine metered-dose inhalers (MDIs) for the treatment of anaphylaxis, but this generally requires large numbers of treatments to obtain meaningful plasma levels, and the safety of inhaled epinephrine at those doses has not been established. Additionally, inhalers require some amount of

proficiency by the user to be effective and may be difficult not only for patients to self-administer correctly if critically ill, but also for rescuers to correctly administer. However, if proven, the use of MDIs would also be a relatively painless way to self-administer treatment for anaphylaxis.<sup>53,54</sup>

As mentioned previously, emergency medical responders (EMRs) are allowed to carry and administer EAIs in 12 states.<sup>37</sup> Currently, there is no training for this in the national curriculum. This may change as political pressures from groups such as the FAAN are urging EAIs to be carried by every EMS agency in the United States, regardless of the level of training. It is important that as EMS agencies and EMS medical directors increasingly allow EMRs to carry and administer EAIs for anaphylaxis, they study and document the training processes, QA programs, and outcomes to further the evidence base that is currently lacking on the out-of-hospital care of anaphylaxis patients. Additionally, there is some recent controversy surrounding the ability and willingness of emergency medical dispatchers (EMDs) to assist callers with the administration of EAIs should the need arise during the course of a 9-1-1 call. Supporters cite a news story where an EAI was successfully administered over the phone during a 9-1-1 call, with the help of an EMD, for a case of presumed anaphylaxis.<sup>55</sup> Critics counter that it would be difficult for callers to accurately identify, during an emergency, the several different brands of EAIs, as each would require unique instructions. It would also be necessary for callers to ensure that the medication was not expired. There is also concern regarding EMDs' ability to accurately diagnose anaphylaxis over the phone and potentially give epinephrine to a patient not experiencing anaphylaxis. There are two different standard doses of epinephrine in EAIs as well, and ensuring that the correct dose was administered may also prove challenging over the phone.<sup>55</sup> The NAEMSP has no recommendation at this time regarding the issue of EMDs' assisting with administration of EAIs, as this is an area that would require further investigation.

## CONCLUSION

Epinephrine is the cornerstone of treatment for the potentially life-threatening condition of anaphylaxis. There are many reasons why EMS agencies that utilize both BLS and ALS providers should be allowed to carry and administer epinephrine. Most anaphylaxis occurs in the out-of-hospital environment, and delayed treatment worsens morbidity and mortality. Patients and caregivers often are unaware of how to properly use EAIs, frequently carry expired EAIs, and do not carry their EAIs at all times. Anaphylaxis may require more than one treatment, and epinephrine enjoys an excellent safety profile when given by the IM route.

Anaphylaxis is both underrecognized and undertreated. Continuing medical education as well as EMS medical director involvement will be instrumental in allowing EMS agencies to successfully and safely use epinephrine for those with anaphylaxis.

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