

# Underuse of epinephrine for the treatment of anaphylaxis: missed opportunities

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**Abstract:** Epinephrine is the only effective treatment for anaphylaxis but studies routinely show underutilization. This is especially troubling given the fact that fatal anaphylaxis has been associated with delayed administration of epinephrine. Many potential barriers exist to the proper use of epinephrine during an anaphylactic reaction. This article will explore both patient- and physician-related factors, as well as misconceptions that all contribute to the underuse of epinephrine for the treatment of anaphylaxis.

**Keywords:** anaphylaxis, epinephrine, emergency department, food allergy

## Introduction

Although epinephrine is the only effective treatment to prevent progression of an anaphylactic reaction,<sup>1</sup> its underuse has been reported in many studies.<sup>2-7</sup> Fleischer et al found that only 30% of severe allergic reactions were treated with epinephrine in a cohort of preschool children with known food allergy.<sup>7</sup> Robins et al found that almost two-thirds of patients presenting to a tertiary care pediatric emergency department (ED) had not received epinephrine prior to arrival at the ED.<sup>5</sup> This pattern is concerning given that most cases of reported deaths from anaphylaxis have been associated with delayed administration of epinephrine.<sup>8,9</sup> Many potential barriers surround the proper use of epinephrine during an anaphylactic reaction. This article will explore both patient- and physician-related factors, as well as misconceptions that can all contribute to the underuse of epinephrine for the treatment of anaphylaxis.

## Patient barriers

### High cost of epinephrine prescriptions

Recently, much attention has been given to the increasing cost of epinephrine auto-injectors (EAIs). In 2016, the average wholesale price of 2 EpiPens exceeded \$700, an increase of 545% from 2007.<sup>10</sup> Similarly, another article reported the price for an EpiPen to be >\$600 in 2016.<sup>11</sup> EAIs may be prohibitively expensive for many patients without health insurance/prescription coverage or for patients with high deductible insurance plans.

Patient assistance programs have been put in place to attempt to reduce the burden of purchasing injectable epinephrine, but cost still remains a significant concern for many patients. The high cost has resulted in consideration of sub-optimal modes of epinephrine delivery, such as the use of pre-filled syringes or expired autoinjectors. Although both of these approaches are better than not delivering any epinephrine, they raise concerns.<sup>10,12</sup>

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Pre-filled syringes require more training, are more likely to be associated with handling or dosing errors, are more sensitive to ultraviolet light and temperature extremes, and must be replaced every 2–3 months.<sup>10</sup> Expired EAI's have been shown to deliver a lower dose of epinephrine. However, the exact amount of viable epinephrine remaining in expired devices ranges from 51–90%, depending upon time since expiration and study methodology used.<sup>12–14</sup>

## Lack of epinephrine availability among patients

Many studies have demonstrated that patients, even when prescribed epinephrine, do not have it available to use during anaphylaxis. Curtis et al found that <60% of patients presenting to an allergy clinic for food allergy follow-up visit had their personal epinephrine device available.<sup>15</sup> This is concerning, as this group of patients receiving subspecialty care should presumably have more education and awareness of food allergy management. Brooks et al reviewed the electronic record of all food allergy reactions presenting to a pediatric tertiary care ED and found that less than half of the patients with a known food allergy had epinephrine present at the time of the reaction.<sup>6</sup>

## Lack of epinephrine availability in schools and camps

Most people do not know of their food allergy until they experience their first allergic reaction. Up to 25% of food allergic reactions within schools occur in children with no previous food allergy.<sup>4</sup> In addition, even when patients do know about their food allergy, many fail to bring their EAI's with them to school.<sup>16</sup> Given the vast amount of time children spend at school, epinephrine availability within schools has been a high priority for food allergy advocacy organizations and parents of food allergic children. Recent legislative efforts have led to passage of laws throughout the USA that allow for voluntary stocking and use of EAI's within schools, but only 12 states mandate procurement.<sup>17</sup> Current implementation of this legislation has not been studied or evaluated on a widespread basis. The lack of EAI's may be even more problematic in the camp setting. One study found that less than half of students with reported food allergies attending a summer camp brought their EAI with them to camp.<sup>18</sup>

## Lack of epinephrine use, even when available

In addition to lack of availability, many patients may not use their EAI, even when it is available during an anaphylactic reaction. This can occur for a variety of reasons, including

lack of the following: recognition of anaphylaxis, knowledge with regard to indications for use of epinephrine, or comfort using epinephrine. The training that each patient receives with regard to recognition of anaphylaxis will be variable and dependent upon the information provided by their personal clinician, their own online searches, or discussion with other patients and families. Hence, it is easy to recognize the variability in the amount and reliability of information received by each individual patient. In a national registry of patients with peanut and tree nut allergy, a consistent inability to recognize anaphylactic symptoms was found.<sup>19</sup> Sheikh et al also demonstrated that even when patients with a reported episode of anaphylaxis carried an EAI, many did not use it at the time of their reaction.<sup>20</sup> Robinson et al reported more encouraging data and found that when available, 86% of children received epinephrine prior to arrival at the ED and those patients with multiple food allergies were more likely to use their epinephrine.<sup>5</sup> Brooks et al, however, found that when epinephrine was available, only about two-thirds of patients used it to treat an anaphylactic reaction.<sup>6</sup> Reasons for not using their epinephrine included as follows: not thinking it was necessary, fear of using it, or having an expired device.

## Incorrect technique

An additional barrier to the proper use of epinephrine is lack of proper training with regard to correct technique. Bonds et al found that 84% of patients with previous prescriptions for EAI's could not demonstrate accurate technique.<sup>21</sup> Ridolo et al also identified a low rate of proper demonstration of epinephrine technique at follow-up visits, with only 39% of patients demonstrating proper technique.<sup>22</sup> Training in proper technique is the responsibility of the prescribing clinician. This should entail a careful review of how each device operates, hands-on instructions, and time during the office visit to practice with a training device, including feedback on patient performance. Proper technique should be reviewed with a training device at every subsequent office visit and patient errors should be addressed. With limited time during office visits, physicians may not be able to perform this training, but ancillary staff, including nurses, can be a valuable resource in this realm. Clinicians can also direct patients toward online resources that have been vetted for accuracy.

Epinephrine is a life-saving medication and proper use during an anaphylactic reaction is of paramount importance. However, as described previously, there are many potential barriers to correct administration of epinephrine by patients – they must receive a prescription for the medication, must be able to purchase (afford) the medication, must have the

medication available, must recognize when to use the medication, and must be able to use the device appropriately. Each of these steps represents an area of much-needed improvement.

## Physician barriers

When evaluating physician prescribing habits and use of epinephrine for the treatment of anaphylaxis, it is clear that there is a need for improvement in this area as well. As previously mentioned, delayed administration of epinephrine in the treatment of anaphylaxis is associated with increased mortality,<sup>9</sup> and consensus guidelines recommend epinephrine as first-line therapy.<sup>1,23,24</sup> Despite this, antihistamines and corticosteroids are often the first medications administered by physicians to patients presenting with anaphylaxis.<sup>25–27</sup> Even more concerning is that several recent studies demonstrate that approximately half of patients presenting to the ED with anaphylaxis never receive epinephrine.<sup>26,28–31</sup> Please see Box 1 for a summary of several relevant articles and key Fast Facts surrounding physician barriers to proper treatment.

## Complexity of diagnosing anaphylaxis

One potential physician barrier for the appropriate use of epinephrine is the complexity involved in establishing the diagnosis of anaphylaxis. Anaphylaxis is a clinical diagnosis with no confirmatory diagnostic tests available. While a serum tryptase obtained within 1–6 hours of symptom onset can be helpful in confirming the diagnosis of anaphylaxis, it has a low sensitivity, particularly in food-induced ana-

phylaxis.<sup>24</sup> Furthermore, given the rapidly progressing and severe nature of anaphylaxis, waiting for laboratory results, particularly a serum tryptase level, will delay necessary treatment.

In order to simplify the diagnosis, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) assembled an international and multidisciplinary panel in 2006 to establish clinically relevant criteria to more clearly define anaphylaxis.<sup>1</sup> This panel defined 3 separate clinical scenarios in which criteria for making the diagnosis vary depending on the likelihood of a patient's exposure to a potential allergen, Box 2. The NIAID/FAAN criteria were subsequently validated in the ED setting and were shown to have a sensitivity and specificity of 96.7% and 82.4%, respectively.<sup>32</sup> While these criteria are widely accepted among consensus guidelines, a recent survey of 207 ED providers in the USA reported that only 9% of providers used agreed-upon clinical criteria to diagnose anaphylaxis.<sup>33</sup> Moreover, while the NIAID/FAAN criteria are helpful in research and education, there is some concern that their low positive predictive value of 69% makes them less useful for ED physicians who have to maintain a broad differential diagnosis.<sup>34</sup> Nevertheless, the NIAID/FAAN criteria appear to have improved the diagnosis and management of anaphylaxis among at least some ED physicians with 1 study demonstrating an increase of intramuscular (IM) epinephrine administration by 40% after the criteria was established.<sup>28</sup>

### Box 1 Fast facts

- Only 8% of patients diagnosed with drug-induced anaphylaxis in the ED were given epinephrine and only 18% of this population were evaluated by an allergist/immunologist in the 1 year following their reaction.<sup>31</sup>
- Implementation of an anaphylaxis order set increased the rate of epinephrine administration in the ED by ~20%.<sup>45</sup>
- The NIAID 2006 guidelines for the treatment of anaphylaxis have improved the treatment of management of anaphylaxis with one pediatric ED showing a significant increase in the rate of epinephrine use via the IM route from 6% to 46%. However, only 61% of patients received EAI's upon discharge with no significant change with implementation of the guidelines. There was a significant increase in allergy referrals; however, still, only 48% of patients received referrals post guideline.<sup>28</sup>
- In adult patients seen in the ED, drugs are the most common cause of anaphylaxis and several studies demonstrate that less than half of patients diagnosed with anaphylaxis receive epinephrine.<sup>29</sup>
- A retrospective chart review of pediatric patients diagnosed with anaphylaxis in the ED showed that only 56% of patients received IM epinephrine and 63% of these patients received a prescription for an EAI. Referral to an allergist was made in only 33% of cases.<sup>33</sup>
- While physicians might assume that epinephrine injection is a cause for increased patient stress, a recent study demonstrated that in patients experiencing anaphylaxis, epinephrine use was actually associated with an increased quality of life.<sup>40</sup>
- While there is no one specific diagnostic test to identify anaphylaxis, The NIAID/FAAN criteria were validated in the ED to have a sensitivity of 96.7% and a specificity of 82.4%.<sup>32</sup>
- Only 38% of patients suspected of having anaphylaxis in the ED had documented follow-up by an allergist, and 35% of these patients had an alteration in the diagnosis and/or trigger of anaphylaxis.<sup>49</sup>

**Abbreviations:** EAI, epinephrine autoinjector; ED, emergency department; FAAN, Food Allergy and Anaphylaxis Network; IM, intramuscular; NIAID, National Institute of Allergy and Infectious Disease.

**Box 2** Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is very likely when any one of these 3 criteria are met:

Acute onset (within minutes to 3 hours) of rapidly progressive symptoms involving the skin, mucosal tissue, or both (examples include: generalized hives, pruritus, flushing, swollen lips or tongue) and at least one of the following:

- Respiratory symptoms (dyspnea, wheezing, stridor)
- Hypotension or associated symptoms of end-organ dysfunction (syncope, collapse)

Two or more of the following that occur rapidly after likely exposure to an allergen (within minutes to 3 hours):

- Skin-mucosal involvement (generalized hives, pruritus, flushing, swollen lips or tongue)
- Respiratory symptoms (dyspnea, wheezing, stridor)
- Hypotension or associated symptoms of end-organ dysfunction (syncope, collapse)
- Gastrointestinal symptoms (vomiting, crampy abdominal pain)

Reduced blood pressure after exposure to known allergen for that patient (within minutes to 3 hours)

- This scenario most often involves a patient with known environmental allergies who received an allergen immunotherapy subcutaneous injection immediately prior

## Lack of knowledge about epinephrine administration

Another potential physician barrier for the appropriate use of epinephrine in the management of anaphylaxis is the lack of knowledge of how to administer epinephrine and use EAI. There is clear evidence that IM administration of epinephrine in the anterolateral thigh achieves faster and higher peak plasma concentrations compared with administration via the subcutaneous route.<sup>35,36</sup> Despite this, many physicians choose either a subcutaneous or intravenous (IV) route of delivery.<sup>28,37,38</sup> In addition to decreased efficacy, administration of epinephrine via the incorrect route is associated with an increased likelihood of overdose and subsequent cardiovascular complications.<sup>38,39</sup> Confusion also likely arises from the variety of autoinjectors available, each of which have a different technique, as well as different concentrations of liquid epinephrine available for use in the hospital setting. Misconceptions about epinephrine safety, which will be more extensively discussed later in this article, may also contribute to physician underuse. Interestingly, while physicians might assume that an epinephrine injection may cause increased patient stress, a recent study demonstrated that in patients experiencing anaphylaxis, epinephrine use was associated with increased patient quality of life.<sup>40</sup>

The use of EAIs in the treatment of anaphylaxis has helped in decreasing some of the adverse outcomes associated with improper administration of epinephrine, yet studies have demonstrated that not all physicians know how to correctly use EAIs.<sup>41,42</sup> Furthermore, the lack of physician familiarity of EAIs along with inadequate patient instruction appears to be associated with improper patient use of EAIs.<sup>42-44</sup> The advent of new EAIs that have attempted to

simplify their use with audible instruction, may help to improve correct administration; however, formularies may limit which EAIs are available for patients to obtain through their insurance provider. Implementation and emphasis of EAI education as a part of physician training programs has likely increased familiarity among providers; however, more recent studies need to be performed to confirm this. One possible intervention that may help in improving the appropriate use of epinephrine in patients diagnosed with anaphylaxis within the emergency setting is the use of electronic order sets. For instance, Manivannan et al demonstrated that the implementation of an anaphylactic order set significantly increased the rate of appropriate epinephrine administration by 18%.<sup>45</sup>

## Low EAI prescription rates for patients at high risk for future anaphylaxis

The low rate of EAI prescriptions given to patients who are at high risk of future anaphylaxis is another physician barrier that warrants improvement. Since most episodes of fatal anaphylaxis occur outside the hospital setting, current guidelines recommend that patients who are at high risk for future episodes of anaphylaxis be prescribed EAIs and instructed on their use.<sup>23,24</sup> Despite this recommendation, multiple studies have demonstrated that most patients diagnosed with anaphylaxis in the ED do not receive EAI prescriptions, with actual percentages of patients receiving prescriptions ranging from 8% to 63%.<sup>26,28,29,46,47</sup> This is a significant barrier when considering that Pourang et al reported that when an EAI prescription was provided, it was dispensed 95.9% of the time, independent of copay amount.<sup>47</sup> To further complicate this issue, some patients who would benefit from having an

EAI prescription are not diagnosed with anaphylaxis initially. This is commonly observed in patients presenting with isolated cutaneous symptoms secondary to an immunoglobulin E-mediated food allergy. Given the risk of accidental exposure and potential for severe anaphylaxis, many experts have recommended prescribing EAIs for these patients in addition to those presenting with more apparent anaphylaxis.<sup>48</sup> Finally, unless a prescription for an EAI is labeled “Dispense as Written”, individual states may allow pharmacies to substitute one device for another, without any confirmation from the prescribing clinician. Substitutes are typically chosen according to insurance formularies and medication coverage. Given the differences in technique with each device, such changes could result in errors in administration if proper technique is not reviewed at the time of substitution.

### Low rates of allergy referrals for patients at high risk for future anaphylaxis

A final physician barrier for the appropriate use of epinephrine in the management of anaphylaxis is the low rate of referral to an allergist/immunologist. While a referral for further evaluation will not directly impact the acute management of anaphylaxis, it can have significant implications on the long-term management of patients at high risk of future anaphylaxis. One recent study demonstrated that 35% of patients referred to allergy/immunology had an alteration in the diagnosis of anaphylaxis or the eliciting trigger of the patient’s prior reaction.<sup>49</sup> Effective prevention of future anaphylaxis relies upon avoidance of known triggers, thus proper identification of relevant allergens is paramount to successful patient care.

Studies have also demonstrated that patients who received consultation with an allergist were 6 times more competent in demonstrating how to appropriately use an EAI,<sup>4</sup> but unfortunately, patients with a history of severe anaphylaxis were less likely to have been evaluated by an allergist.<sup>50</sup> Despite the clear benefits of an allergy referral, the majority of patients diagnosed with anaphylaxis in the ED are never evaluated by an allergist/immunologist.<sup>26,28,31,46,49</sup>

### Misconceptions surrounding epinephrine

As discussed earlier in this article, there are many variables that contribute to whether epinephrine is used in the treatment of anaphylaxis. In addition to physician prescribing habits, lack of proper education and training of patients, and lack of availability of devices due to financial constraints or nonadherence, there are several misconceptions that may also

contribute to underuse of epinephrine. The origins of these misconceptions are either unknown or multifaceted, and the pervasiveness is not fully understood. However, both patients and health care providers are subject to both receiving and disseminating misinformation. This section will discuss common misconceptions as well as the surrounding evidence that refutes them.

#### Misconception #1: epinephrine should not be used in anyone with a history of cardiovascular disease

Epinephrine is a nonselective agonist of all adrenergic receptors, which can induce several cardiovascular effects, including increased peripheral resistance (vasoconstriction) via  $\alpha_1$  receptors and increased cardiac output via  $\beta_1$  receptors. Epinephrine has important cardiac inotropic and chronotropic effects that help in reversing the symptoms of anaphylaxis.<sup>48</sup> In addition, the package insert for epinephrine indicates many potential adverse effects, including angina, arrhythmias, and rapid rise in blood pressure, with potential for cerebral hemorrhage. It is readily apparent why health care professionals and patients with a history of cardiovascular disease may approach to use epinephrine with caution.

Recent evidence demonstrates that adverse cardiovascular events associated with epinephrine use during anaphylaxis are relatively rare and almost always associated with improper dosage or administration. A review of 301 patients who received at least 1 dose of epinephrine for anaphylaxis at a large tertiary care ED demonstrated a total of 4 overdoses and 8 adverse cardiovascular events.<sup>38</sup> All 4 overdoses and 50% of the adverse effects occurred after IV bolus dosing of epinephrine. Among 245 patients who received epinephrine through IM autoinjector use, 1 had angina and 2 experienced hypertension. The authors identified a significantly higher risk of adverse events (odds ratio [OR] 7.5 [95% CI, 1.6 to 35.3]) and overdose (OR 53.4 [95% CI, 6.5 to infinity]) when epinephrine was administered by IV compared with IM administration.

A similar retrospective review of 492 patients found that risk of adverse event from epinephrine administration almost exclusively occurred in adult patients who received IV dosing (OR 99.6 [95% CI, 7.4 to infinity]).<sup>39</sup> Among patients in this cohort who received IM epinephrine, 3.5% of older patients experienced cardiovascular complications compared with 0.5% of younger patients (OR 1.09 [95% CI, 0.65 to infinity]). Collectively, these data demonstrate relatively low risk for cardiovascular complications from IM use of epinephrine in preloaded autoinjectors. It also demonstrates

inappropriate use of IV epinephrine in the hospital setting, which dramatically increases risk for side effects. Published guidelines on management of anaphylaxis support use of IV bolus epinephrine only when a patient has ongoing hypotension despite multiple doses of IM epinephrine and IV fluid resuscitation, or if they are in cardiovascular arrest.<sup>23</sup> Thus, the misconception with regard to cardiovascular complications from epinephrine appears to originate from complications arising from IV administration, and not from the use of autoinjectors.

Interestingly, cardiac complications can rarely arise during the pathophysiologic process of anaphylaxis, which are separate from epinephrine. Kounis syndrome is a rare condition that manifests as acute vasospastic coronary syndrome secondary to the inflammatory mediators released during an acute allergic reaction.<sup>51</sup> Kounis syndrome has been reported in individuals with and without underlying coronary artery disease.

### Misconception #2: EAls cannot be used in infants

Currently, there are only 2 premeasured doses of epinephrine, 0.15 and 0.3 mg, in autoinjectors available in the USA and Canada.<sup>48</sup> Manufacturers recommend use of the 0.15 mg dose for patients weighing 15–30 kg and the 0.3 mg dose for anyone weighing  $\geq 30$  kg. However, expert consensus suggests switching most children from the 0.15 mg to the 0.3 mg dose when they reach a body weight of 25 kg.<sup>52</sup>

Two issues arise in infants weighing  $< 15$  kg: proper dosing and needle length. The 0.15 mg dose is 2-fold higher than recommended for infants  $\leq 7.5$  kg.<sup>53</sup> However, no alternatives are available other than drawing up 0.1 mg of epinephrine in a vial and having caregivers administer this in place of the autoinjector. The risk of dosing error, inappropriate administration, and degradation within a few months due to air exposure<sup>54</sup> likely outweighs the risk of using the 0.15 mg preloaded autoinjector, hence most experts agree with the latter approach.

A recent study raised concern about potential for intraosseous injection of epinephrine in young children weighing 15–30 kg due to needle length.<sup>55</sup> The authors used ultrasound to measure the distance from skin to muscle and bone on the anterolateral thigh in 102 children weighing 15–30 kg. They found that use of high pressure 0.15 mg autoinjectors was associated with 11% risk of intraosseous injection for Epipen Jr and Auvi-Q/Allerject (Canadian version of Auvi-Q) devices and 38% risk through use of Jext (European version of Adrenaclick). A similar study using ultrasound to measure

depth on the anterolateral thigh evaluated infants weighing  $< 15$  kg.<sup>56</sup> This study identified 19% of infants 10–14.9 kg and 60% of infants  $< 10$  kg at risk for intraosseous injection of 0.15 mg Epipen Jr and Allerject.

Epinephrine is the only effective and first-line treatment for anaphylaxis. In 2017, the US Food and Drug Administration granted priority review and approval for the production of a 0.1 mg autoinjector, but until this is more widely available, the only commercial option for infants weighing  $\leq 15$  kg is a 0.15 mg dose. Given the importance of prompt administration of epinephrine for the treatment of anaphylaxis, all infants at risk for anaphylaxis should have an autoinjector prescribed. However, parents and caregivers should be counseled on potential risks involved with dosing and needle length, within the context of providing effective therapy for a potentially life-threatening reaction.

### Misconception #3: EAls are harmful

Many parents fear using EAls on their children as they are afraid it may cause injury or harm them.<sup>7,57</sup> A review of voluntary self-report to the USA Poison Control Centers identified 15,190 unintentional injections from EAls between 1994 and 2007.<sup>58</sup> Among those injured, 57% were aged  $< 18$  years, including 18% aged  $\leq 5$  years. Only 15.2% of reported injuries were moderate or severe, indicating need for treatment, and 75% of all reported injections resulted in very minor symptoms that self-resolved. Of note, only 40% of unintentional injections occurred when the person was trying to inject themselves or another person during an allergic reaction. Other occurrences were during: inspection of the device (13%), disposal of the device (11%), a training session (8%), or when reaching into an enclosed space such as a purse or bag (7%).

A recent retrospective case series reported 22 cases of EAI-related injury among children, all from the Epipen Jr or Epipen devices.<sup>59</sup> Requests for cases were queried from email discussion lists and social media groups, thus the incidence of such injuries could not be determined. Seventeen (77%) of the injuries involved leg lacerations and 4 (18%) involved retained needles. Ages of the children involved ranged from 1 to 11 years (mean=4.6 years). All 17-reported lacerations occurred on the lateral thigh and ranged in length from 1.5 to 8 inches. Among these, only 3 (18%) required sutures. All cases that included details of administration noted that the children kicked or moved their leg during epinephrine administration. Interestingly, this study helped in changing Epipen manufacturer instructions from a previous 10-second hold time to 3 seconds,

with the goal of reducing risk from injury due to children moving their legs.

Most health care providers who have prescribed EAI's have anecdotal reports of unintentional injection of themselves, colleagues, or their patients. Limited published data support that this likely does occur to some extent, but the true incidence is unknown. However, evidence suggests that any harm from unintentional injection is likely minimal and can be avoided through proper training and supervised practice with a medical provider. The misconception that autoinjectors are harmful likely stems from anecdotal reports and parental concerns, which should not preclude use, when indicated.

## Misconception #4: epinephrine is dangerous, so if you use it, you need to go to the ED

This section has already addressed common misconceptions surrounding adverse effects and injury from EAI's. However, many parents or patients may be reluctant to administer epinephrine given the recommendation to always call 911 or seek emergency medical care. This can be viewed as unnecessary and inconvenient by some. Others may misconstrue the necessity of emergency room evaluation due to the dangers of the medication itself, as opposed to the need for monitoring and potential need for additional treatment due to the allergic reaction.

All published guidelines on the management of anaphylaxis recommend assessment at an ED after treatment with epinephrine in the community setting.<sup>23,52,60</sup> This recommendation stems from concern that symptoms may continue to progress and require additional therapy, or due to risk of biphasic anaphylaxis.

Very few patients who experience anaphylaxis require hospitalization due to ongoing treatment or monitoring. The decision to admit after emergency room evaluation is individualized and consideration should be given to any patient who requires more than 1 dose of epinephrine and/or IV fluids due to hypovolemic shock, experiences laryngeal edema, has a history of severe or poorly controlled asthma, or biphasic anaphylaxis.<sup>61</sup> These factors will often present during a 4–6 hours observational period in the emergency room (or prior to arrival), thus the recommendation for transport and observation.

Biphasic anaphylaxis is a recurrence of anaphylactic symptoms after initial resolution despite no additional exposure to the trigger. Previous reports suggested that this occurs in roughly 20% of anaphylactic episodes. However, a recent meta-analysis reveals that this likely occurs in ~5% of cases

of anaphylaxis and is more likely to occur with initial severe symptoms or when anaphylaxis is not treated with epinephrine in a timely manner.<sup>62</sup> It is well documented that patients, emergency responders, and even emergency room physicians do not always treat anaphylaxis with epinephrine, instead using antihistamines and/or corticosteroids.<sup>61</sup> Unfortunately, these medications are not effective in treating anaphylaxis and should never be used in place of epinephrine.

Patients who may have the misconception that ED evaluation is necessary due to the side effects from epinephrine, should be counseled about the need for monitoring and potential for progression of symptoms

## Conclusion

Multiple studies across a variety of perspectives have demonstrated a universal theme: Epinephrine is underused in the treatment of anaphylaxis. Now that there is a solid basis of research demonstrating the need for improvement, we need interventional studies and quality improvement approaches to drive change. There are many areas in need of improvement and it will take an ongoing concerted effort to see any positive changes. Improvement in these areas begins with increasing awareness among health care providers, patients, and the general public as well.

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## Author contributions

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