



Epinephrine in anaphylaxis: too little, too late

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Purpose of review

Epinephrine is the agreed-upon first line treatment for anaphylaxis, yet it continues to be underused by patients/caregivers and providers alike.

Recent findings

There are unfortunately limited data on how epinephrine can best be utilized in anaphylaxis, which hinders how best to inform patients and providers. Studies reporting underuse suggest various barriers and themes on why this may happen.

Summary

Continued education of patients, caregivers, and providers is needed; however, is not likely to be enough to close the gap. Thus, novel studies on how to increase use; increase availability in a cost-effective manner; and newer, effective delivery routes are still needed.

Keywords

anaphylaxis, carriage, epinephrine, food allergy, underuse

INTRODUCTION

There is no accepted, single definition of anaphylaxis. In fact, amongst recent anaphylaxis guidelines, the only words that consistently appear in anaphylaxis definitions are ‘life-threatening, systemic reaction’ [1]. Despite the lack of uniformity in the definition of anaphylaxis, all major anaphylaxis guidelines state that epinephrine is the only first-line therapy for the treatment of anaphylaxis [2–4,5^{***},6^{***}]. This is based mainly on two factors. First, via its effects as a nonselective adrenergic agonist, the pharmacologic action of epinephrine is thought to reverse key physiologic consequences of anaphylaxis (e.g. vasodilation, mucosal edema, hypotension, and bronchoconstriction) [5^{***}]. Second, is that lack of use or a delay in epinephrine administration has been associated with anaphylaxis fatalities [7]. Despite this, data continue to suggest that epinephrine is underutilized [7]. In this review, we discuss data supporting the use of epinephrine in anaphylaxis, available data on timing of administration and outcomes, data suggesting poor adherence to guidelines and possible reasons why, and hopeful strategies to mitigate these issues.

DATA SUPPORTING THE USE OF EPINEPHRINE IN ANAPHYLAXIS

Given that all guidelines suggest epinephrine as the only first-line therapy for anaphylaxis, one might

assume that there are overwhelming data to support this. Unfortunately, however, this is not the case. In fact, it has been well documented that there are no randomized or placebo-controlled studies examining epinephrine in the management of anaphylaxis [8]. Due to the lack of evidence, the most recent 2020 United States Practice Parameter guideline on anaphylaxis recommended the use of epinephrine as a ‘good practice statement’ recommending to ‘administer epinephrine as the first-line pharmacotherapy for uniphasic and/or biphasic anaphylaxis’ [5^{***}]. In an accompanying article, the authors acknowledged that good practice statements were made when there is high certainty that the recommendation will do more good than harm, but little or no direct evidence [6^{***}].

Overwhelming support for the use of epinephrine then is mainly based upon the known pharmacologic actions of epinephrine, some animal data, and few observational and retrospective human

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KEY POINTS

- Available data, mainly from cohort studies, suggest that delay in administration of epinephrine in anaphylaxis can be associated with increased mortality and morbidity.
- Despite agreement in all major guidelines, epinephrine continues to be underused by both patients/caregivers and practitioners alike.
- Increasing epinephrine use in anaphylaxis is likely to require a multifaceted approach, with education being only one of these approaches.

studies. Via its actions on α -1 receptors, epinephrine can increase vascular resistance reversing mucosal edema, hypotension, and shock; via action on β -1 receptors, it can increase cardiac output; and via action on β -2 receptors, it can lead to bronchodilation. These are all ideal effects in the treatment of anaphylaxis [9].

Unfortunately, though the actual animal and human data to support these actions are not as concrete.

Animal studies

There are a few well designed animal studies examining the role of epinephrine in the treatment of anaphylaxis. In a ragweed-induced canine anaphylaxis model, epinephrine when given intravenous after maximal hypotension was able to transiently increase mean arterial resistance and stroke volume as compared with placebo [10]. However, intramuscular and subcutaneous epinephrine did not alter hemodynamics at all when compared with placebo. This early study suggested that epinephrine had minimal effect once hemodynamic collapse occurred.

In a follow-up study in the same ragweed-induced canine model, administration of epinephrine via different routes was studied when given at the initiation of allergen challenge rather than once hypotension peaked [11]. Results from this study showed that only constant infusion of epinephrine (not intravenous bolus, intramuscular, or subcutaneous routes) led to significant changes in mean arterial pressure or cardiac output compared with no treatment.

Similar findings have been observed in an ovalbumin-induced rat model, in which epinephrine given by intravenous bolus $\times 2$ after the onset of shock, followed by continuous infusion, improved hemodynamics and survival, with no effects seen with saline bolus followed by infusion [12,13]. Data

from these studies indeed suggest that epinephrine can restore cardiovascular function in animal models of anaphylactic shock; however, to achieve meaningful clinical effects, it must be given by continuous intravenous infusion, a route rarely used in the management of anaphylaxis in humans.

Human studies

As mentioned earlier, there are no randomized clinical trials of epinephrine for anaphylaxis in humans, thus information on the utility of epinephrine in outcomes of anaphylaxis can only be gleaned from examining outcomes from other means.

Perhaps the best reports are from older, small, prospective studies examining sting challenges in placebo-controlled venom immunotherapy studies [14,15]. In these studies, many patients who received placebo immunotherapy developed anaphylaxis upon sting challenge. In the older study, Smith *et al.* showed that 11/14 patients who reacted had initial cutaneous symptoms that responded to epinephrine. However, 3/14 patients developed immediate hypotension, and only 1 of these responded to epinephrine [14]. Brown *et al.* showed that all 21 patients with systemic reactions to sting challenge responded to epinephrine. However, it is important to note that all patients were treated with intravenous epinephrine at doses higher than typically provided to patients and for prolonged time (mean dose 590 μ g and 115 min). In addition, those patients with hypotension required even higher doses for longer infusions (mean dose 762 μ g and 169 min) [15]. Thus, from these studies, it appears epinephrine can treat anaphylaxis, but may require higher doses and intravenous form in severe reactions.

DATA SUPPORTING EARLY ADMINISTRATION OF EPINEPHRINE

The more common way that the role of epinephrine in anaphylaxis treatment is assessed is by examining large databases of anaphylaxis or smaller cohorts of severe or fatal anaphylaxis. From the early case fatality studies by Sampson and Pumphrey, there seems to be a theme that there was a delay in administration of epinephrine in fatal anaphylactic reactions [16,17]. Table 1 highlights findings from more recent selected cohort/database studies of anaphylaxis in which epinephrine administration was reportedly associated with outcomes.

It is important to understand, however, that reporting a low incidence of use or delayed administration of epinephrine in a cohort of fatal cases does not infer causality, especially when we do not know

Table 1. Select cohort studies examining effect of (early) epinephrine

Reference	Population	Definition of early epinephrine	Outcome
Sampson <i>et al.</i> [16]	Six fatal and 7 'near-fatal' food-induced, pediatric anaphylaxis cases	Not defined	Near-fatal cases received epinephrine earlier than fatal cases. No patient who died received epinephrine before severe respiratory symptoms developed
Pumphrey [17]	Registry of 164 all-cause fatalities because of anaphylaxis	Not defined	Only 20% of those given epinephrine received this before they arrested
Xu <i>et al.</i> [18]	Ninety-two deaths because of all-cause anaphylaxis from a single Canadian Province	Not known; however, documented if given 'prior to cardiac arrest'	Authors concluded 'delayed' epinephrine was associated with fatal anaphylaxis cases (however, there were no controls and no data on timing of administration)
Fleming <i>et al.</i> [19]	384 ED visits to a children's hospital for food-induced anaphylaxis	Receipt of epinephrine before arrival to the emergency department	Significantly decreased risk of hospitalization in patients who received early epinephrine versus late epinephrine
Hochstadter <i>et al.</i> [20]	965 ED visits to a children's hospital for all cause anaphylaxis	Receipt of epinephrine before arrival to the emergency department	Early administration of epinephrine associated with a decreased likelihood of requiring multiple doses of epinephrine in the ED
Andrew <i>et al.</i> [21]	2137 pediatric all-cause anaphylaxis patients seen by EMS Australia	Receipt of epinephrine before EMS arrival versus receiving epinephrine after EMS arrival	Patients receiving early epinephrine (versus after EMS arrival) were more likely to present with vital signs in the normal range
Dorris [22]	70 deaths because of food-induced anaphylaxis (early US registry data)	Not defined	Author stated the when details were available, most fatal cases had delayed or no epinephrine use

the percentage of patients with milder reactions who got epinephrine and when.

As described above, many of the fatal case series concluded that delay in administration of epinephrine was a risk for fatal anaphylaxis [16–18,22]. However, the key flaw in that conclusion is that we do not know the outcome had they gotten epinephrine earlier and we do not have comparator groups in most studies who survived where times of epinephrine administration relative to symptom onset were well documented.

From the studies examining nonfatal outcomes, there are signals to suggest that early administration of epinephrine can decrease hospitalizations or possibly severity of reactions (based on surrogate markers) [19–21]. Thus, there are some data to argue that early epinephrine can at least decrease morbidity if not mortality from anaphylaxis.

DATA SUGGESTING POOR ADHERENCE TO EPINEPHRINE USE

Despite the guidance and evidence above, studies show that, in patients presenting with anaphylaxis, epinephrine use either prehospital and/or in the emergency department is suboptimal, and this

occurs throughout the world [21,23[■],24–27,28[■],29[■],30,31], Table 2).

Rates for epinephrine use will vary by study due several factors (geographic location, population studied, reports of ED and/or pre-ED use, severity of cases selected, etc.); however, it is clear that many patients presenting with anaphylaxis never receive epinephrine, which may have several underlying reasons.

REASONS FOR LOW UTILIZATION OF EPINEPHRINE

There are numerous reasons for underutilization of epinephrine. On the provider side, these can be broken down into themes, such as gaps in knowledge,

Table 2. Selected national/international studies reporting epinephrine use in anaphylaxis

Location	Trigger	Percentage receiving epinephrine
Europe [23 [■]]	All cause	27%
United States [28 [■] ,29 [■]]	Food [29 [■]] Venom[28 [■]]	56% 49%
China [25]	All cause	14%

lack of implementation, and lack of follow-up care [26]. Gaps in knowledge can be attributable to poor anaphylaxis recognition, poor knowledge of treatment choices, or poor knowledge of adequate dosing, which can be easily defined by knowledge assessment tools [26]. Lack of implementation is less easily defined. This may exist when providers are knowledgeable about anaphylaxis and the treatment but choose not to give epinephrine. Separating knowledge from real life actions is challenging. For example, one study showed that implementing an order-set and a 1-h education session in one ED, led to improvements, but epinephrine use only increased from 33 to 51% [32]. Understanding reasons for this is difficult. For example, even when allergists are surveyed, there are gaps in when they would consider a case anaphylaxis but choose not to treat with epinephrine [33]. Finally, lack of follow-up care suggests patients with an anaphylactic event are not given prescriptions for autoinjectors or not referred to a specialist for follow-up care, and therefore, may not be prepared for future reactions [24,26,34,35].

Like providers, for patients, lack of knowledge (e.g. confusion on the diagnosis of anaphylaxis or lack of understanding of autoinjector device) may be one factor that leads to underuse of epinephrine. However, patients/caregivers face other obstacles that likely affect their use of epinephrine. These can be outlined as follows.

Not having epinephrine autoinjector available

This has been a theme affecting anaphylaxis management for years [26]. One major global hurdle is that autoinjectors are still not readily available worldwide [36]. However, even in patients prescribed an autoinjector, surveys continue to show poor prescription fill and carriage rates [37–39].

Having epinephrine available but not using it during reaction

This issue does not appear to be as common as lacking the autoinjector during a reaction. However, based on survey results, there are patients who had an autoinjector available, but did not use during a severe reaction. Most commonly this was because of the patient/caregiver not considering the reaction serious; other reasons were because of lack of understanding of how to use the device or fear of the medication or that it would escalate the situation [38,40].

Underdosing of epinephrine

Even if epinephrine is administered, there is a concern that in some cases the dose may not be

adequate. There are no dose-ranging studies of epinephrine in anaphylaxis, but guidelines suggest an intramuscular dose of 0.01 mg/kg to a maximum of 0.5 mg in adults and 0.3 mg in children [5²²]. Given current epinephrine autoinjectors have limited dosing options, there is clearly a likelihood that the dose will be inadequate in some patients [41]. In addition, given that needle lengths are not adjustable, there is a chance that in some patients, the device will deliver the medication subcutaneous rather than intramuscular [42,43].

MOVING THE IMMOVABLE OBJECT

Defining the problem and understanding the causes, as undertaken above, will hopefully allow for some improvement in epinephrine usage. To date, studies examining trends in epinephrine use are inconsistent, with some showing increase use of epinephrine and others showing no change over years, but as stated earlier, rates are still lower than desired [28²,29²,32,44,45].

Thus, measures should still be taken to improve this.

Improving knowledge of anaphylaxis management and the role of epinephrine

Common sense would suggest that increasing knowledge of anaphylaxis would increase epinephrine use; however, there are essentially no data to show that this is true.

Identification of anaphylaxis is the first step in the process, and efforts have gone into improving knowledge surrounding this area, yet gaps remain amongst providers and patients/caregivers alike. The current working, clinical definition of anaphylaxis proposed in the United States was meant to identify clinical cases where epinephrine is warranted [46]. Indeed, these criteria have been shown to be highly sensitive, but not very specific [47]. As introduction of these criteria there has been only a small change in delivery of care [28²,29²]. In fact, one single-center study did show improved usage of epinephrine by the desired intramuscular route (versus subcutaneous) in their ED after publication of these guidelines; however, no changes to overall epinephrine use was seen [45].

Specific forms of education on anaphylaxis hold promise as well. Simulation studies, for example, can show immediate postsimulation knowledge gained via testing strategies but unfortunately there are no outcomes studies to show that this can change clinical practice [48,49]. Education sessions or videos can also increase knowledge and confidence of treatment for both providers and caregivers

[50,51], but this is only assessed by pretest and posttest scores and not by any clinically meaningful outcomes.

Anaphylaxis action plans are designed to guide the patient/caregiver in recognition and anaphylaxis, thus streamlining the decision-making process for them [52]. Unfortunately, the effectiveness of these action plans has never been tested.

Thus, as clinicians, we need better ways to assess whether simple education can make a difference in outcomes and if so, what type of education is most effective and how often re-education would be needed.

Increasing availability of epinephrine

As discussed earlier, not all areas of the world have access to epinephrine autoinjectors, and whenever available, epinephrine is not always filled, carried or used. Cost is a major factor in extending availability, and this issue is not easily fixed [53]. One attempt to address this concern is to allow 'stock' epinephrine in public places, such as schools, airplanes, and other community locations. Currently, there are little data to show how effective this can be, though some data generated from modeling studies demonstrate potential cost-effectiveness but little real-world data to show the utility of this approach [54–57].

Increasing carriage of autoinjectors

Increasing carriage of the device when available is difficult. Investigators have attempted methods, such as text reminders and even financial incentives; however, these appear to have little overall effect or may not be feasible on a large scale [58,59]. One study noted that the type of auto-injector device may influence carriage, suggesting that convenience may play a role in carriage [60]. Thus, at this point, clinicians are left without much data to suggest any specific means that have been proven to increase carriage rates.

Increasing routes of delivery of epinephrine

Currently, epinephrine is recommended to be used by the intramuscular route with intravenous infusion for more severe, intractable cases. There are other routes of administration being studied currently, such as intranasal and sublingual epinephrine [61,62]. These routes hold promise, as there is an assumption that removing the barrier of a needle, will hopefully increase the likelihood that epinephrine will be used by patients (although this has not been proven). Currently, data on the intranasal form has only been published as an abstract [62]. Questions remain whether regulatory agencies will approve these medications based on bioequivalence data to the intramuscular form, as it is very unlikely

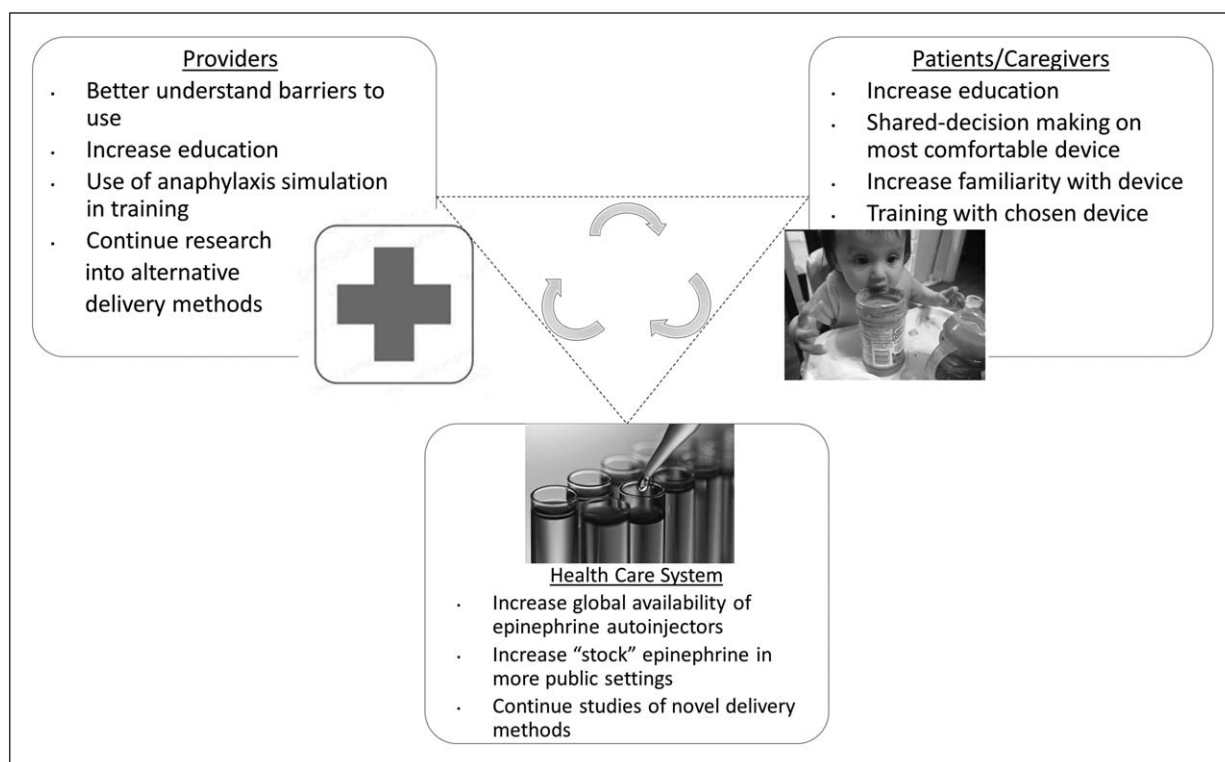


FIGURE 1. Multifaceted approach to improving epinephrine use in anaphylaxis.

they will be able to be studied against either placebo or intramuscular form in the clinical setting (i.e. a placebo-controlled or head-to-head study in anaphylaxis).

CONCLUSION

Epinephrine remains underused both by the patient/caregiver and the provider. There are several reasons contributing to this gap in care, some of which can be summarized in Fig. 1. Unfortunately, there are sparse data to truly guide us on how epinephrine can best be used, and thus breaking down these barriers to use is difficult. Although continued education is an easy suggestion, education alone will not likely close the gap significantly. Thus, novel studies on how to increase use; increase availability in a cost-effective manner; and newer, effective delivery routes are still needed.

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Conflicts of interest

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