

Pitfalls in the use of epinephrine for anaphylaxis: patient and provider opportunities for improvement

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Background: Epinephrine remains the mainstay of treatment for life-threatening allergic reactions. A number of challenges are encountered with epinephrine, resulting in underutilization and misutilization of epinephrine. The purpose of this study was to identify the scope of epinephrine pitfalls and opportunities for improvement in the management of allergy emergencies.

Methods: A PubMed search from 1990 to 2015 was performed to identify all cases and reports pertaining to the use and misuse of epinephrine for anaphylaxis. Studies were assessed for obstacles or complications related to proper administration of epinephrine for treatment of allergic reactions, and were divided into problems originating with patients compared to healthcare providers.

Results: There were 1840 publications related to epinephrine use, of which 61 reports met inclusion criteria for pitfalls in the use of epinephrine. The most common problems reported related to lack of autoinjector availability (22), inadequate education of patients or providers (9), uncertainty about when or how to administer epinephrine (9), concern for systemic effects (13), failure to adminis-

ter (8), and accidental administration (2). Responsibility for errors was divided among patients (18), providers (39), or both (4).

Conclusion: Epinephrine is a potent medication with life-saving indications and is the standard of care for treatment of anaphylaxis. The delivery of epinephrine in both trained and untrained populations carries certain pitfalls and complications that can have serious consequences. Identification of the scope of the problem is an important step in improving education for both providers and patients who are tasked with use of epinephrine for allergy emergencies. © 2016 ARS-AAOA, LLC.

Key Words:

allergy immunotherapy; allergy injections; health care economics; pediatric allergy; epinephrine; anaphylaxis

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Anaphylaxis is a life-threatening emergency that requires immediate treatment to avoid catastrophic outcomes. The mainstay of treatment for anaphylaxis is intramuscular (IM) epinephrine: a powerful adrenergic agonist

that has known pitfalls and potential side effects (Table 1). Anaphylaxis can occur during routine allergy treatment in a monitored setting in patients undergoing allergy testing or immunotherapy, or in an unmonitored setting such as at home with a new food allergy. Guidelines recommend that patients who had a severe reaction and are at risk for anaphylaxis in the future receive a prescription for an epinephrine autoinjector (EAI) with instructions for its use.^{1,2}

Although epinephrine is widely acknowledged as the treatment of choice for anaphylaxis³ it continues to be underutilized, a fact demonstrated in a variety of settings. White et al.⁴ performed a web-based survey of 6019 schools that participated in the EpiPen4Schools program and found that out of nearly 1000 events, approximately 25% of individuals with anaphylactic events were not treated with EAI. Manivannan et al.⁵ analyzed use of epinephrine by emergency medical services (EMS) transport personnel and

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TABLE 1. Pitfalls in the administration of epinephrine

Pitfall	Result
Failure to administer/re-dose	Progression of anaphylaxis
Administration without anaphylaxis/ accidental administration	Side effects of epinephrine
Incorrect dosing (pediatric vs adult)	Inadequate treatment or overdose
Epinephrine not readily available	Progression of anaphylaxis
Complication or epinephrine side effect	Hypertension, cardiac
Interaction with medications (ie, MAOIs)	Hypertension, cardiac
Wrong site of injection	Damage to terminal vascular organs
Failure to monitor post-reaction	Recurrence of anaphylaxis
Failure to re-dose during reaction	Progression of anaphylaxis
Inadequate education for patients/providers	All of the above
Cost/lack of availability	Epinephrine is not used

MAOI = monoamine oxidase inhibitor.

found that it was used in less than 20% of cases of suspected allergic reactions, although not all these patients displayed signs of full anaphylaxis. Alvarez-Perea et al.⁶ found that only 40% of patients presenting to a tertiary-level emergency department with signs of anaphylaxis were treated with epinephrine, while Vezir et al.⁷ found similar rates in a pediatric allergy clinic.

Given the apparent underutilization of epinephrine and the dual responsibilities of providers and patients to provide emergent treatment with epinephrine in the setting of anaphylaxis, this study was undertaken to evaluate the problems associated with epinephrine use which may limit its use, as well as the opportunities for improvement in the emergent treatment of severe allergic reactions.

Materials and methods

An English language PubMed search was performed on March 1, 2016, using permutations of epinephrine, adrenaline, anaphylaxis, allergic reaction, complications, allergist, and autoinjector. All search results were mined for data relating to the use of epinephrine for treatment of allergic reactions. The results were evaluated for any pitfalls in appropriate epinephrine administration and barriers surrounding the use of epinephrine in anaphylaxis. Reports where epinephrine was used to treat an allergic reaction without complication, comprehensive reviews detailing the role of epinephrine as a first line agent to treat anaphylaxis, and reports on low usage of epinephrine that did not attempt to describe reasons for failure were excluded. Assessment of the primary responsibility of error to the patient or the provider was assigned to each report to identify opportunities for improvement in care.

Results

A total of 1840 results from PubMed were returned on initial search. Sixty-one unique reports met inclusion criteria and included over 33,000 patients or providers who administered epinephrine for allergic reactions. Reports described challenges in the use of epinephrine, including: lack of EAI availability (22), inadequate training of patients or providers on use of an EAI (9), uncertainty about when or how to administer epinephrine (9), concern for systemic effects of epinephrine (13), failure to administer (8), and accidental injury (2) (Fig. 1).

Of reports on lack of EAI availability (22), 10 assigned fault to the patient, finding failure to fill or refill prescriptions, or carry a prescribed EAI, while 9 assigned responsibility to providers; generally these were reports from different emergency department settings finding low rates of EAI prescription and/or lack of referral to allergy specialists (Table 2). One of the reports assigned responsibility to both patients and providers. Two reports used high rates of EAI prescription by allergy providers to emphasize the need for referral to a specialist. Two reports assessed failure of institutions to provide EAI.

In reports of concern for the systemic effects of epinephrine, only a single case report resulted from patient administration, whereas 12 case reports and 1 large cohort study reported on provider administration (Table 3).

Nine reports evaluated patients or providers on their ability to use or train others to use an EAI (Table 4); 5 of these assessed the efficacy of training patients and found that while training is effective, the benefits of training dissipate quickly with time. Four reports found consistent lack of knowledge among providers in their ability to train patients to use EAI.

Nine reports evaluated different provider's lack of knowledge on administration and dosing of epinephrine (Table 5). Two reports found inconsistent use of epinephrine by providers in simulation studies with a failure to correctly diagnosis anaphylaxis or recognized epinephrine as the preferred treatment. This was confirmed by an observational study in an emergency department, which found less than 50% of patients who presented with signs and symptoms meeting diagnostic criteria for anaphylaxis were diagnosed as such, leading to less than 40% of patients receiving epinephrine. Five studies of patients determined uncertainty about when to use or fear of using an EAI contributed to failure to use (Table 6).

Reports on accidental injection or injury found that while these more commonly occurred in patients, 18% occurred in providers (Table 7). Errors in the use of EAI were equally divided between patients and providers among all categories of EAI pitfalls, with the exception of reports of systemic responses to epinephrine, which were almost all related to provider administration. When these 13 reports were removed, 17 assigned responsibility to the patient while 27 assigned responsibility primarily to providers and 4 assigned to both.

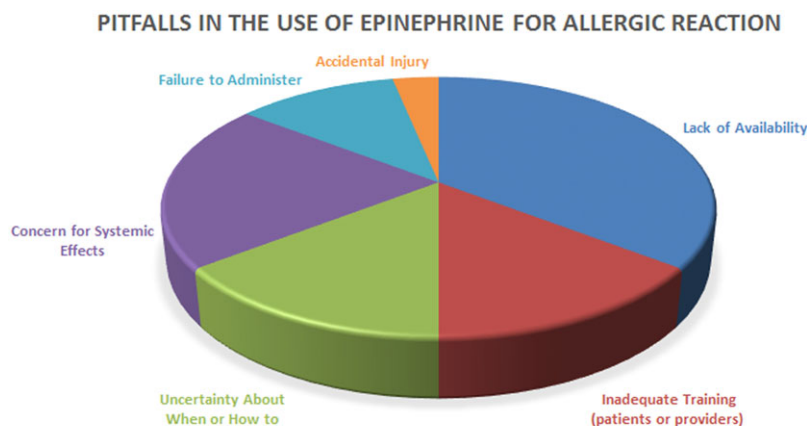


FIGURE 1. The number of publications that identified problems in the use of epinephrine for the treatment of severe allergic reactions.

Discussion

Epinephrine is a lifesaving treatment for anaphylaxis, yet it also carries substantial risk for misuse. Anaphylaxis is demonstrated to have increased risk of fatal outcomes when epinephrine administration is delayed; therefore, its proper and timely administration is paramount.^{8,9} With the need for such rapid treatment, patients are tasked with providing the EAI treatment themselves. It is somewhat unique to have patients being responsible for administration of a powerful medication with serious side effects that is used in emergency situations only. Even with years of medical training, clinicians encounter difficulties and pitfalls with the use of epinephrine, yet patients are carrying the same burden for emergent use of this drug and device.

Epinephrine

Epinephrine is lifesaving in the treatment of anaphylaxis and it should be given as soon as possible to prevent the progression to life-threatening symptoms.¹⁰ Because of its narrow therapeutic index, epinephrine can cause a multitude of transient side effects such as anxiety, tremor, headache, restlessness, palpitations, pallor, dizziness, and tremor. In patients with cardiovascular risk factors, hyperthyroidism, or in patients taking monoamine oxidase inhibitors/tricyclic antidepressants, epinephrine may lead to severe side effects such as myocardial ischemia/infarction, ventricular conduction abnormalities, pulmonary edema, malignant hypertension, and intracranial hemorrhage.¹¹ Serious side effects are also common after intravenous (IV) bolus administration. However there are no contraindications to the use of epinephrine in the setting of anaphylaxis.¹²

Autoinjector availability

Despite the rise in prevalence of both allergic diseases and anaphylaxis, there has not been the corresponding increase in the awareness of the need for readily available EAIs that has been realized for cardiac treatment with automated external defibrillators. In 2013, the federal School

Access to Emergency Epinephrine Act was signed into law. This amended the Public Health Service Act, with respect to asthma-related grants for child health services, to give an additional preference to a state that allows self-administration of asthma and anaphylaxis medications and requires schools in these states to (1) maintain an emergency supply of epinephrine; (2) permit trained personnel of the school to administer epinephrine; and (3) develop a plan for ensuring trained personnel are available to administer epinephrine during all hours of the school day.¹³ Although an emergency supply of epinephrine could presumably be used for patients without known allergies, studies have shown that nearly one-half of students prescribed an EAI did not have the device at school.¹⁴ Shah et al.¹⁵ found that despite 97% of Houston elementary schools reporting students with food allergies, only 43% stocked EAIs. A larger number of injectors in schools were associated with students of higher socioeconomic status. Olympia et al.¹⁶ performed a survey of U.S. summer camps and found that only 64% reported having immediately available EAIs. States and cities have taken steps recently to address this issue; the Nevada State Legislature recently mandated that all schools in Nevada have stock epinephrine available.

In addition to lack of publically available epinephrine, patients often do not have EAIs, even when indicated. Landsman-Blumberg et al.¹⁷ found only 54% of patients seen in an emergency department for food-induced anaphylaxis filled a prescription for an EAI within 1 year, while Rudders et al.¹⁸ found only 69% of patients seen for stinging insect anaphylaxis filled their prescription. Johnson and Parker¹⁹ found that patients over 55 years old and patients who received their EAI prescription from an outpatient clinic as opposed to an emergency department were more likely to fill the prescriptions.

Beyond filling initial prescriptions, Kaplan et al.²⁰ evaluated nearly 15,000 patients in a health maintenance organization (HMO) over a 6-year period and found that less than 50% refilled their EAI even once and that only

TABLE 2. Reports showing lack of availability of epinephrine for treatment of allergic reactions (n = 22,577 patients)

Authors	n	Pitfall	Summary	Responsibility
Amirzadeh et al. ²³ (2010)	66	Availability	Observational study in a VA Allergy clinic found only 58% of patients carried their EAI consistently	Patient
Asero et al. ³⁴ (2010)	1100	Availability	EAI prescribing by Italian allergy specialists in patients with food allergy; history of anaphylaxis or ED visits were predictive of being prescribed an EAI	Provider
Ben-Shoshan et al. ¹⁴ (2008)	271	Availability	Questionnaire study found less than 50% of children with peanut allergy did not carry EAI with them at school	Patient
Braganza et al. ³² (2006)	57	Availability	Retrospective records review in a pediatric emergency department in Australia; EAI prescribed to 17.5% and 28% were referred to an allergist	Provider
Campbell et al. ³⁰ (2008)	208	Availability	Retrospective records review in 2 community EDs; EAI prescribed to 36.6% of patients and 31.3% were referred to an allergist	Provider
Clark et al. ²⁷ (2004)	678	Availability	Review study in 21 North American EDs with patients seen for food allergies; EAI prescribed to 16% and referral to an allergist was recommended to 12%	Provider
Clark et al. ²⁸ (2005)	259	Availability	Review of insect sting visits at 15 North American EDs; EAI prescribed to 27% and referral to an allergist was recommended to 20%	Provider
DeMuth and Fitzpatrick ²² (2011)	63	Availability	Observational study in a pediatric allergy clinic found 59% of food allergic children had EAI present in the clinic	Patient
Fineman et al. ³³ (2013)	500	Availability	Survey of members of American College of Allergy, Asthma, and Immunology found 95% report prescribing EAI	Provider
Flokstra-de Blok et al. ³⁶ (2011)	23	Availability	Random screening of Dutch adolescents found only 2 of 23 candidates with food allergy were prescribed EAI	Provider
Haymore et al. ³¹ (2005)	24	Availability	Retrospective review identified 24 patients with anaphylaxis; EAI prescribed in 29% of cases with instruction on its use documented in 13% and 29% were referred to an allergist	Provider
Johnson and Parker ¹⁹ (2006)	769	Availability	Retrospective review of EMR in a military medical center assessed characteristics of patients more likely to fill EAI prescription	Patient
Kaplan et al. ²⁰ (2011)	14,677	Availability	Database analysis on the refill history of patients in an HMO who received initial dispensing of an EAI found only 46% refilled at least once, and only 11% refilled consistently at expected times	Patient
Landsman-Blumberg et al. ¹⁷ (2013)	1370	Availability	Retrospective records review of patients treated in an ED for anaphylaxis just over 50% filled prescription for EAI	Patient
Mugica-Garcia et al. ³⁵ (2015)	887	Availability	Found that only 30% of patients with prescribed EAI used them during episodes. Only 67% of patients prescribed EAI filled the prescription	Patient
Olympia et al. ¹⁶ (2015)	–	Availability	Survey of U.S. summer camps; 64% had available EAI	Provider
Rudders et al. ¹⁸ (2013)	954	Availability	Retrospective records review of patients seen in ED for stinging insect anaphylaxis; 69% filled EAI prescription, but only 14% had 1 or more allergist/immunologist visits	Both
Russell et al. ²⁹ (2010)	124	Availability	Retrospective records review of anaphylaxis in a tertiary care pediatric ER; EAI prescribed to 63% and referral to an allergist was recommended to 33%	Provider
Sanchez ²¹ (2013)	120	Availability	Questionnaire of patients prescribed an EAI; 57.5% had epinephrine in their house or office; 27.5% had it at a visit 6 months after being prescribed	Patient
Schwartz ²⁶ (1995)	326	Availability	One-year survey of patients seen in an ED for anaphylaxis; EAI prescribed to 27% bee sting allergic patients and 12.5% were referred to an allergist	Provider
Shah et al. ¹⁵ (2014)	–	Availability	Presence of absence of EAI in Houston elementary schools; One or more children with food allergies were reported in 97% of responding schools, but only 43% of schools reported having epinephrine injectors. There were 6 times more injectors in non-low SES schools than in low SES schools	Provider
Sicherer et al. ²⁴ (2000)	101	Availability	Questioned 101 families of food allergic children; 55% had unexpired EAI on hand	Patient

ED = emergency department; EAI = epinephrine autoinjector; EMR = _____; ER = emergency room; HMO = health maintenance organization; SES = socioeconomic status; VA = Veterans Administration.

TABLE 3. Reports showing problems with systemic effects of epinephrine for treatment of allergic reactions (n = 589 patients)

Authors	n	Pitfall	Summary	Responsibility
Ameratunga et al. ⁶⁰ (2008)	1	Systemic effects	Unstable angina after receiving IM epinephrine for anaphylaxis; 4 weeks later had 2nd episode of anaphylaxis and suffered cardiac arrest after receiving IV epinephrine bolus	Provider
Anchor and Settupane ⁶⁷ (2004)	2	Systemic effects	Two reports of IV epinephrine resulted in transient adverse cardiac events	Provider
Arfi et al. ⁶⁶ (2005)	1	Systemic effects	Ischemic changes on ECG and elevated cardiac enzymes after inadvertent IV epinephrine for allergic reaction to IVIG	Provider
Campbell et al. ⁷⁰ (2015)	573	Systemic effects	Observational cohort of patients treated for anaphylaxis found 4 overdoses with IV administration and 0 with IM; rates of adverse events were 1.3% with IM dosing vs 10% with IV dosing	Provider
Cunnington et al. ⁶² (2013)	1	Systemic effects	Ischemic chest pain and electrocardiographic changes, associated with troponin elevation, following IM epinephrine for anaphylaxis	Provider
Davis and Wax ⁶⁹ (1999)	1	Systemic effects	Ventricular dysrhythmias and myocardial ischemia in a 5-year-old boy who received 10× recommended subcutaneous dose of epinephrine	Provider
Kanwar et al. ⁷² (2010)	4	Dosing	Four reports of accidental cardiac (ie, IV) dosing in patients with anaphylaxis	Provider
Khoueiry et al. ⁶³ (2013)	1	Systemic effects	Stress cardiomyopathy following high-dose IV epinephrine for mild anaphylaxis	Provider
Magri et al. ⁶⁴ (2011)	1	Systemic effects	Stress cardiomyopathy following IM epinephrine injection	Provider
Palma et al. ⁷¹ (2012)	1	Systemic effects	Reversible cerebral vasoconstriction syndrome following the administration of IM epinephrine for anaphylaxis	Provider
Park et al. ⁶¹ (2015)	1	Systemic effects	Acute MI due to stent thrombosis after receiving IV epinephrine for anaphylaxis	Provider
Saff et al. ⁶⁸ (1993)	1	Systemic effects	MI after self-administration of an Epi-Pen	Patient
Shaver et al. ⁶⁵ (2006)	1	Systemic effects	Vasospasm-induced myocardial injury with IV epinephrine	Provider

ECG = electrocardiogram; IM = intramuscular; IV = intravenous; IVIG = intravenous immunoglobulin.

11% refilled consistently at all expected refill times. Several studies performed over the last 15 years have consistently shown that only 50% to 60% of patients carry their EAI with them regularly and can produce them at their office visits.^{21–24}

Although seemingly intuitive, the importance of patients having an EAI was further demonstrated by Fleming et al.,²⁵ who found that among 384 patients presenting to a pediatric emergency department for food-induced anaphylaxis, patients owning an EAI were more likely to receive epinephrine before reaching the emergency department.

Patients may fail to fill prescriptions, but it is the providers' responsibility to make sure an EAI is initially prescribed, and to follow up to ensure patients have obtained them. In 1995, Schwartz²⁶ found that only 27% of patients seen in an emergency department for stinging insect anaphylaxis were given an EAI and only 12.5 were referred to an allergist.

Unfortunately, more recent studies in the last 10 years of patients seen in a range of emergency departments for anaphylaxis from various causes show little improvement in the frequency of referral to an allergist, ranging from 12% to 33%. There has been some evidence that of an increase

in prescription of an EAI, although the rate varies widely from 16% to 69%, and is still far less than needed.^{18,27–32}

Furthermore, follow-up care is essential. Fineman et al.³³ surveyed members of the American College of Allergy, Asthma, and Immunology via an online questionnaire and found that >95% reported prescribing EAI and instructing patients on their use. Asero et al.³⁴ similarly found that 89% of patients with history of food-allergy anaphylaxis seen in Italian allergy clinics were prescribed EAI. However, even among specialists, prescription rates vary. Mugica-Garcia et al.³⁵ surveyed 887 patients treated in an outpatient allergy clinic in Spain for anaphylaxis and found significant variations in the prescription rates for EAI, ranging from 21.5% for food anaphylaxis up to 72% of patients who had anaphylaxis induced by hymenoptera venom. Flokstra-de Blok et al.³⁶ found less than 10% of food allergic Dutch children who were candidates for an EAI based on their answers to a questionnaire had been prescribed one.

Failure to use

In the survey by Mugica-Garcia et al.,³⁵ they also found that only two-thirds of patients who were prescribed an

TABLE 4. Reports of lack of training for epinephrine use for an allergic reaction (n = 1441 patients)

Authors	n	Pitfall	Summary	Responsibility
Arga et al. ⁵² (2011)	156	Training	Evaluation of effectiveness of training residents; assessed knowledge of EAI use in pediatric residents; prior to training <25% could use correctly	Provider
Brown et al. ⁴³ (2013)	100	Training	Prospective evaluation of 100 random mothers; after training 15% still unable to use correctly	Patient
Grouhi et al. ⁵¹ (1999)	122	Training	Survey of providers in fields that commonly prescribe an EAI found only 25% could correctly demonstrate the “three steps” of injection	Provider
Quercia et al. ⁴² (2014)	400	Training	Prospective study found that 80% of trained patients could correctly use EAI vs 10% untrained on a controlled test	Patient
Salter et al. ⁵⁰ (2014)	271	Training	Simulated patients to assess pharmacists ability to assist patients in management of anaphylaxis; 17.3% of pharmacists correctly demonstrated the epinephrine autoinjector	Provider
Segal et al. ⁴⁵ (2012)	141	Training	Observational study found poor retention on how to use an EAI even by the first follow up; 38% failed to remove the cap before trying to apply the device; scores improved by 50% after reinstruction at second visit	Patient
Sicherer et al. ²⁴ (2000)	29	Training	Survey of prescribing MDs found only 24% gave written instructions and only 18% could demonstrate device use	Provider
Topal et al. ⁴⁶ (2013)	64	Training	Observational study 1 year after receiving an EAI only 39% were still competent in use; there was a significant relation EAI competency and regular allergy visits	Patient
Umasunthar et al. ⁴⁴ (2015)	158	Training	Prospective evaluation mothers of food allergic children on ability to correctly use an EAI 6 weeks and 1 year after training; found an 43% success rate	Patient

EAI = epinephrine autoinjector; MD = medical doctor.

EAI purchased one. Among patients who had recurrences, 31% reported that they had used the autoinjector, 32% had not, and 37% reported that they had not received any prescription after their allergy assessment.³⁵

Ensuring that patients and families are able to recognize the signs and symptoms of anaphylaxis is essential. Kim et al.³⁷ found that among parents who did not use an EAI for their child's allergic reaction, “I did not think the reaction was serious,” was the reason given by 50% of parents. Pouessel et al.³⁸ found that of parents with food-allergic children, only 48% were able to cite more than 1 usual symptom requiring use of an EAI.

Similarly, Arkwright et al.³⁹ found that 69% of parents of food-allergic children were unable to use the EAI, did not have it available, or did not know when it should be administered. They also found that practical demonstration was associated with a 4-fold to 5-fold greater chance that parents would be able to use the device, and that prior consultation with an allergy specialist rather than a general physician was also associated with increased competency.

Several studies using questionnaires or simulations have demonstrated low rates of administration by physicians. Klemans et al.⁴⁰ found that in a questionnaire containing hypothetical cases administered to general practitioners in the Netherlands, epinephrine was used for treatment of anaphylaxis with mainly respiratory symptoms in only 27% of cases and for anaphylaxis with mainly cardiovascular symptoms in 73%. O’Leary et al.⁴¹ placed junior

medical staff from an emergency department in a standardized scenario and found only 50% administered epinephrine. This was confirmed by Alvarez-Perea et al.,⁶ who found less than one-half of patients presenting to an emergency department with anaphylaxis were given that diagnosis and only 40% received epinephrine.

Adequacy of education

Quercia et al.⁴² found that 80% of patients who received formal education, consisting of explanation and a practical test, were able to correctly use an EAI in a practical controlled test, as compared to only 10% of untrained patients. Brown et al.⁴³ found similar results when training mothers and then asking them to demonstrate the device—15% were unable to “fire” them correctly. Umasunthar et al.⁴⁴ performed a prospective randomized controlled trial to assess the ability of mothers whose children had been prescribed an EAI to successfully administer epinephrine in a simulated anaphylaxis scenario. They found less than one-half of participants were able to administer adrenaline using a commonly prescribed EAI 6 weeks after completing formal training. They evaluated device design and found that failure to remove both caps and injecting with the incorrect end were common reasons for failure. In contrast, over 90% of participants were able to successfully administer adrenaline using an audio prompting pen without receiving device-specific training. Several other studies have

TABLE 5. Dosing and administration errors in the delivery of epinephrine for allergic reactions (n = 5081 patients)

Authors	n	Pitfall	Summary	Responsibility
Droste and Narayan ⁵³ (2012)	284	Dosing and administration	Survey of 284 hospital doctors in UK found 14.4% (n = 41) would administer epinephrine as recommended by published anaphylaxis guidelines	Provider
Gompels et al. ⁵⁴ (2002)	78	Dosing and administration	Questionnaire of UK senior house officers found 100% would administer adrenaline (epinephrine) but 55% would do so by the incorrect route; only 5% were able to indicate the correct route and dose of adrenaline	Provider
Jacobsen et al. ⁴⁸ (2012)	3537	Dosing and administration	Survey of paramedics found <50% identified epinephrine as the initial drug of choice; only 38.9% chose the IM route of administration	Provider
Jose and Clesham ⁵⁸ (2007)	95	Dosing and administration	Questionnaire of UK junior medical staff found 94% would administer epinephrine as the lifesaving drug of choice, but only 16.8% would administer as recommended	Provider
Lammers et al. ⁴⁹ (2014)	62	Dosing and administration	Simulation study of EMS crews found only 46% delivered the correct dose of epinephrine in an appropriate concentration and route and 20% gave a dose that was ≥ 5 times the correct dose	Provider
Lightfoot et al. ⁵⁷ (2009)	253	Dosing and administration	Survey of radiologists found only 41% provided an acceptable administration route, concentration, and dose; 17% of radiologists provided an overdose	Provider
Lowe et al. ⁵⁶ (2010)	613	Dosing and administration	Survey of Scottish GPs; less than half were personally confident in their use and only one-half would use the UK Resuscitation Council recommended adult dose	Provider
Plumb et al. ⁵⁵ (2015)	68	Dosing and administration	Questionnaire of junior level UK physicians found 100% recognized need for epinephrine in anaphylaxis but only 74% selected the correct intramuscular route, and only 34% the correct route and dose	Provider
Thain and Rubythor ⁵⁹ (2007)	91	Dosing and administration	Questionnaire of New Zealand physicians found 92% would administer epinephrine as the lifesaving drug of choice, but only 20% would administer it as recommended and 43% would use more than 5 $\times$ recommended dose	Provider

EMS = emergency medical service; GP = general practitioners; IM = intramuscular.

demonstrated poor retention even by the second visit⁴⁵ and after 1 year.⁴⁶

Lack of patient education contributes to overall fear around use of the EAI. Chad et al.⁴⁷ surveyed patients of children with peanut allergy treated in the allergy clinic of a tertiary children's hospital and found that most parents (56%) expressed fear regarding the use of the EAI, highlighting an important barrier to the management of anaphylaxis. Specific concerns were hurting the child, using the EAI incorrectly, or a bad outcome. Longer disease duration, prior severe reaction, and satisfaction with training were all associated with lower likelihood of being afraid.

It is not only patients who suffer from a lack of knowledge; first responders, who will often be the initial to provider to encounter a patient with anaphylaxis, have been shown to lack knowledge of the appropriate treatments. In a large survey of paramedics, less than 50% identified epinephrine as the initial drug of choice.⁴⁸ A simulation study of 62 EMS crews responding to a pediatric anaphylaxis event, Lammers et al.⁴⁹ found that although 95% of crews administered epinephrine, only 46% delivered the correct concentration and route, with 20% giving a significant overdose and 15% administering via IV bolus.

Salter et al.⁵⁰ used simulated patients to assess pharmacists' ability to assist patients in management of

anaphylaxis and found only 17% were able to correctly demonstrate the use of an EAI.

Among physicians, adequacy of education is a problem as well. In 1999, Grouhi et al.⁵¹ found that among health care providers who commonly prescribe or are responsible for educating patients regarding self-injectable epinephrine (including emergency physicians, pediatricians, and family practitioners), only 25% could correctly demonstrate the "3 steps" of injection (remove safety cap, grasp device, administer into outer thigh and hold in place) and Sicherer et al.²⁴ found only 24% of providers generally gave patients written materials concerning indications for use of an EAI, and only 18% were familiar with and able to correctly demonstrate its use.

Unfortunately, there has been little evidence of improvement in the last 15 years. Arga et al.⁵² found less than 25% of pediatric residents could properly use an EAI prior to a training course. Droste and Narayan⁵³ found in a survey of physicians in England that only 15% would administer epinephrine as recommended by published anaphylaxis guidelines, a small improvement over the 5% who were able to indicate the correct route and dose of adrenaline found by Gompels et al.⁵⁴ 10 years prior. Plumb et al.⁵⁵ surveyed junior doctors in the UK and found that while 74% selected the correct IM route, only 34% the correct

TABLE 6. Reports of complications related to failure to use epinephrine for treatment of severe allergic reaction (n = 3250 patients)

Authors	n	Pitfall	Summary	Responsibility
Alvarez-Perea et al. ⁶ (2015)	118	Failure to use	Observational chart review of patients seen in an ED by an allergy specialist found only 44% of patients fulfilling diagnostic criteria were given diagnosis of anaphylaxis and only 40% of patients received epinephrine	Provider
Arkwright and Farragher, ³⁹ (2006)	122	Failure to use	Questionnaire to assess factors associated with EAI use; 69% of parents were unable to use the EAI, did not have it available, or did not know when it should be administered. Practical demonstrations and consultation with an allergy specialist were associated with increased use	Patient
Chad et al. ⁴⁷ (2013)	1209	Failure to use	Survey of parents whose children were treated in a tertiary care allergy clinic; 56% expressed fear regarding the use of the EAI. Parents attributed the fear to hurting the child, using the EAI incorrectly or a bad outcome	Patient
Kim et al. ³⁷ (2005)	165	Failure to use	Survey of parents of children with food allergy found despite reports of anaphylaxis in 42% of patients only 8% of parents had given EAI	Patient
Klemans et al. ⁴⁰ (2013)	571	Failure to use	Questionnaire of hypothetical cases sent to Dutch general practitioners found epinephrine used anaphylaxis with mainly respiratory symptoms in only 27% and with mainly cardiovascular symptoms in 73%. At discharge, the percentages for prescription of self-injectable epinephrine were 53% and 77%, respectively	Provider
Mugica-Garcia et al. ³⁵ (2015)	887	Failure to use	Found that only 30% of patients with prescribed EAls used them during episodes. Only 67% of pts prescribed EAls filled the prescription	Patient
O'Leary et al. ⁴¹ (2013)	56	Failure to use	Simulated scenarios with junior medical staff from a pediatric emergency department found only 50% of participants administered adrenaline in scenarios of definite anaphylaxis	Provider
Pouessel et al. ³⁸ (2006)	111	Failure to use	Prospective questionnaire study sent to families with a food-allergic child to assess knowledge of symptoms requiring use of EAI found only 48% were able to cite more than 1 usual symptom for use	Patient

EAI = epinephrine autoinjector; ED = emergency department.

TABLE 7. Reports of accidental epinephrine injection (n = 91 patients)

Authors	n	Pitfall	Summary	Responsibility
Brown et al. ⁷⁴ (2016)	22	Injury	Query of emergency medicine discussion list found 22 cases of injuries with EAI use in children; 9 involving health providers and 13 involving parents or patients	Both
Simons et al. ⁷³ (2009)	69	Accidental injection	Review identified 69 unintentional injections over 20 years; 10% occurred in health care providers	Both

EAI = epinephrine autoinjector.

route and dose. Lowe et al.⁵⁶ found that less than one-half of surveyed Scottish general practitioners were confident in their ability to use EAIs and would choose the correct dose and route. Beyond house staff and general practitioners, Lightfoot et al.⁵⁷ surveyed American and Canadian radiologists on knowledge of management of contrast-mediated anaphylaxis and found generally deficient knowledge of epinephrine for the management of severe contrast material-induced allergic reactions. Other questionnaire studies have shown that even when over 90% of physicians recognize epinephrine as the first-line treatment for anaphylaxis, less than 25% could identify the correct dose and route.^{58,59}

Systemic effects

Although there are multiple case reports in the literature of severe cardiac events following use of epinephrine for anaphylaxis,^{60–69} the actual frequency is rare. Campbell et al.⁷⁰ performed an observational cohort study to compare rates of cardiovascular adverse events and overdoses associated with anaphylaxis management between various routes of epinephrine administration among patients in the emergency department. They found that there were no overdoses with 316 doses of IM epinephrine compared with 4 of 30 doses of IV bolus epinephrine. The rate of adverse cardiac events was low: 1.3% with IM epinephrine compared to 10% with IV bolus. In addition to cardiac

events, Palma et al.⁷¹ report a case of reversible cerebral vasoconstriction syndrome. Only a single case report is of an adverse event following patient self-administration of an EAI; the vast majority come from medical providers, often when administering incorrect IV doses.

Kanwar et al.⁷² identified several cases of patients with suspected anaphylaxis receiving inappropriate cardiac arrest dosing of epinephrine (ie, larger doses given IV) with potentially lethal cardiac complications, though all patients ultimately did well. This led them to introduce prefilled and appropriately labeled IM-dosed epinephrine syringes in crash carts, which can be distinguished from IV-dosed epinephrine syringes.

Accidental injection or injury

In 2009, Simons et al.⁷³ reviewed 26 reports totaling 69 cases of accidental injection over the last 20 years. Although 10% of these occurred in healthcare professionals, only 1% occurred in a healthcare setting; most happened in the home or in the community. The vast majority, 98%, involved injection into a digit or palm. The most common symptoms and signs of local ischemia described included pain or numbness, pallor, cyanosis, hypothermia, absence of sensation or hyperesthesia, and weak or absent pulse. A variety of treatments were utilized, from observation to warming the affected body part to local application of nitroglycerin paste to local injections of the α -adrenergic blocker phentolamine. Regardless of treatment modality, most signs and symptoms resolved within 24 hours, and although several patients reported more persistent symptoms including sensory loss and ischemia-reperfusion pain, none developed tissue necrosis. This series reviewed the last 20 years but found that most of the incidents occurred in the last 6 years. Moreover, they concluded the rate of accidental injection is substantially higher than has been reported and the rate of this occurrence is increasing, corresponding to the increased rate of anaphylaxis and the increased rate of prescribing EAI.

Beyond accidental injections, Brown et al.⁷⁴ reported 22 cases of EAI related injuries: 17 lacerations to the patient, 4 cases of retained needles, and 1 case of a laceration to the healthcare provider. Several these occurred during attempted reinjection after the device did not remain in place for the 10 seconds the provider believed was necessary.

Interactions

Other medications can complicate the use of epinephrine and increase the risk of side effects, requiring dose reductions as much as 90%. These include tricyclic antidepressants, which block catecholamine reuptake, increasing the chance of hypertension and arrhythmia. Monoamine

oxidase inhibitors block degradation of catecholamine, increasing the risk of complications when vasopressors such as epinephrine are used. Beta-blockers can prevent some of the beneficial effects of epinephrine and lead to unopposed alpha adrenergic stimulation, causing coronary constriction or exaggerating the pressor effects. Additionally, because beta-blockers may increase the risk of anaphylaxis in patients receiving immunotherapy, many physicians will not start immunotherapy in patients taking these medications. However, this demonstrates the necessity of routine review of patient's medication lists.⁷⁵

Costs

There has been recent media coverage on the increasing prices of EAIs in the United States.^{76,77} From 2003 to 2007, the prices of EAIs across the world slowly increased from an average of US \$70 to US \$97.87. This increase was perceived to be high with respect to the average daily minimum wage, especially taking into account that most countries do not fully subsidize these costs.⁷⁸ In the United States the most popular EAI is the EpiPen, which has been distributed by Mylan pharmaceuticals since 2007.⁷⁹ The EpiPen now commands nearly 90% of the U.S. market on EAIs, with more than US \$1.3 billion in revenue.⁸⁰ As of 2016, a package of 2 EpiPens costs about US \$415, with a shelf life of 1 year.⁷⁹ This 400% increase followed 2010 legislation which recommended that patients with severe allergies have 2 EpiPen on hand instead of 1, as well as the 2013 legislation encouraging states to have epinephrine devices on hand in schools.⁷⁹ The high costs of the EAI may limit availability of patients to obtain devices.

Conclusion

Both patients and providers bear responsibility for the underuse or misuse of epinephrine in the treatment of anaphylaxis. It is the responsibility of providers to prescribe an EAI when indicated, to be able to train patients in their proper use, and to educate patients on the importance of filling these prescriptions and keeping them up to date. Providers should also be aware of available options to help offset the increasing cost of these medications for patients who qualify. Pharmacists, as the main dispensers of EAIs, also have a key role to play in educating patients.⁸¹ Training improves both patient and provider comfort with use of an EAI and increases the odds of patient carrying a device.²² Didactic training,⁸² simulation training,⁸³ and a combination of both methods have been shown to be effective in EAI education.⁵² Given the serious consequences for untreated allergic reactions or misuse of epinephrine, it is important that providers take the lead in improving education for patients with severe allergic reactions. ③

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