Epinephrine autoinjectors for individuals with food allergy: Who, how many, and when to use

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ABSTRACT

Background: *Anaphylaxis is a serious allergic reaction that is effectively treated with epinephrine. Epinephrine autoinjectors are devices that contain fixed doses of medication that can be carried by patients at risk for anaphylaxis so that ready access to first line medication is available outside the medical setting.*

Methods: *This review will discuss recent studies evaluating patient characteristics to consider when prescribing epinephrine autoinjectors.*

Results: *Decisions regarding who should be prescribed epinephrine autoinjectors will depend on the type of allergy, as well as co-morbidities and other risk factors that can increase a patient's risk for poor outcomes.*

Conclusion: *Shared decision-making is essential when developing guidance regarding post-epinephrine management. Regular education during routine follow-up visits can reinforce knowledge and skills for managing food allergy reactions.*

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Epinephrine is the treatment of choice for anaphylaxis, which is a serious allergic reaction that is unpredictable and can occur in any setting.[1] Delayed administration of epinephrine for anaphylaxis has been associated with higher chances for needing additional treatment and for hospitalization.[2,3] Epinephrine autoinjectors (EAI) are devices that contain fixed doses for administration of intramuscular epinephrine that can be prescribed for patients who have a higher risk for anaphylaxis. A prescription for EAIs requires thoughtful consideration because results of studies have suggested that there are negative quality-of-life implications for carrying EAIs and EAIs carry financial costs,[4,5] which supports judicious prescription of these devices.

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WHO SHOULD CARRY EAIs?

International guidelines state that patients at risk for anaphylaxis should be prepared to manage allergic reactions by having EAIs available.[6–8] Determination of risk will depend on atopic disorder and patient history, in addition to situational considerations. Considerations for higher and lower risks of anaphylaxis are shown in Table 1. For example, patients with food allergy can have allergen exposures unexpectedly, so those patients who have a history of systemic allergic reactions have a higher likelihood of requiring EAIs for subsequent reactions. International food allergy guidelines have provided additional allergen- and patient-specific risk factors for EAIs, including treatment with oral immunotherapy, underlying mast cell disorder and/or elevated tryptase, and limited access to medical help.[6–9] Patients with insect sting allergy can have variable risk. A history of only large local or cutaneous systemic reactions or patients on maintenance venom immunotherapy (VIT) or who have completed a 5-year course of VIT with no high-risk factors could be considered to have a lower likelihood of requiring EAIs. Factors that would increase the likelihood for persons with venom allergy to need an EAI include those with a history of anaphylaxis not treated with VIT or who are on VIT but had systemic reactions during treatment as well as patients with allergy to honeybee, an elevated basal tryptase level, or frequent exposure to stinging insects.[1] There may be patients who are at risk for anaphylaxis but are unlikely to have accidental allergen exposures, *e.g.*, drug allergy, so these patients would generally not require EAIs.

Table 1 **Higher likelihood of requiring epinephrine autoinjectors***

IgE-mediated food allergy: previous systemic allergic reaction
Pollen food allergy syndrome: history of anaphylaxis
Venom or insect bite and/or sting allergy
History of anaphylaxis, not treated with a complete course of VIT
Current VIT, with a history of previous systemic reaction(s) to VIT
Honeybee allergy
Elevated basal tryptase level
Frequent exposure to stinging insects
Latex allergy, with occupational exposure
Drug allergy, with occupational exposure
Exercise-induced anaphylaxis
Cold-induced urticaria
Aeroallergen immunotherapy: history of systemic reaction(s) to AIT and/or relevant comorbidities (*e.g.*, asthma)
Idiopathic anaphylaxis
Systemic mastocytosis

IgE = Immunoglobulin E; VIT = venom immunotherapy; AIT = allergen immunotherapy.
**Adapted from Ref. 1.*

HOW MANY EAI DEVICES?

The 2023 anaphylaxis practice parameters suggest that the number of EAIs prescribed should take into consideration a patient's risk factors for severe anaphylaxis, their values and preferences, and contextual factors.[1] Unlike in the United States, EAIs can be prescribed as a single device in Canada, so deliberate decision-making to prescribe one versus multiple devices is a standard consideration. In the United States, the discussions often center on how many devices patients are advised to carry when they are away from home or whether two-pack EAIs can be split for different locations.[1] The practice parameter suggests that more than one EAI be prescribed for patients who have previously required multiple doses of epinephrine to treat an episode of anaphylaxis and/or have a history of biphasic reactions.

The majority of anaphylaxis cases resolve with one dose of epinephrine, but anaphylaxis can be severe enough to warrant multiple doses. A systematic review and meta-analysis of 86 studies (36,557 anaphylaxis events) found that 7.7% (95% confidence interval, 6.4–9.1%) of events were treated with more than one epinephrine dose.[10] In 2.2% (95% confidence interval, 1.1–4.1%) of cases, three or more doses of epinephrine were administered.

Biphasic anaphylaxis reactions are characterized by a second wave of symptoms that fulfill anaphylaxis criteria that develop after the initial symptoms have completely resolved in the absence of re-exposure to the allergen trigger.[11] These new or recurrent symptoms can occur within 1 to 48 hours of complete resolution of the initial anaphylaxis. Studies report that ~5% of anaphylaxis events will be a biphasic reaction.[12,13] Delayed administration of epinephrine has been identified as a risk factor for biphasic reactions.[13] Therefore, having more than one EAI device available to treat allergic reactions is prudent.

Emergency action plans traditionally have incorporated the instruction to call 911 and/or activate emergency medical services (EMS) immediately after epinephrine has been administered because severe reactions may require further medical attention.[1] Patients do not consistently follow this guidance because of the burdens of emergency department (ED) visits (*e.g.*, time, finances, logistics of childcare and/or work). Some patients misconstrue the link between epinephrine and ED visits and believe the epinephrine is not safe, thus warranting ED evaluation after administration. Still other patients erroneously think that if they do not want to seek ED care, then they should avoid using the EAI. Therefore, there has been an effort to make clear to patients and families that the decision to administer epinephrine is a separate decision from calling 911 and that epinephrine is a safe medication, with no absolute contraindications for use. A cost-effectiveness analysis that compared immediately activating EMS after epinephrine use with a watchful waiting approach before activating EMS found that ED observation for a treated, resolved peanut allergy reaction has minimal benefit and excessive costs.[14] The risks versus benefits of ED observation shifted during the COVID-19 (coronavirus disease 2019) pandemic because EDs were overwhelmed and the concern for COVID infection risk, and discussions of home management of anaphylaxis gained traction.[15,16] The updated 2023 practice parameters[1] state that immediate activation of EMS may not be required if the reaction responded promptly and completely with

Table 2 **Questions to consider during shared decision-making for home management of anaphylaxis***

Does the patient have a history of severe anaphylaxis treated with more than two doses of epinephrine, hospitalization, or intubation?
Does the patient have access to at least two EAI and someone to provide help if needed?
Does the patient understand the signs and symptoms that warrant epinephrine use?
Does the patient have an anaphylaxis treatment plan available?
Does the patient know how to use the EAI and is willing to use it?
Does the patient feel comfortable with home management?
Does the patient have good adherence to previous treatment recommendations and plans?

EAI = Epinephrine autoinjector.
**Adapted from Ref. 16.*

epinephrine, so long as the patient has additional EAI available and can access medical care if needed. Certainly, families may choose to activate EMS whenever they feel the need, even if the reaction seems to be successfully treated. However, if anaphylaxis is severe, fails to resolve promptly, fails to resolve completely or nearly completely, or returns or worsens after a first dose of epinephrine, then activation of EMS is suggested. The decision for home management of anaphylaxis will vary from patient to patient and from reaction to reaction for any given patient. Some factors to consider as clinicians engage in shared decision-making with patients and families are listed in Table 2.

Antihistamines and glucocorticoids have no role in the acute management of anaphylaxis,[17] and the 2020 anaphylaxis practice parameters suggest against the use of antihistamines or glucocorticoids to prevent biphasic anaphylaxis.[18] Antihistamines can improve skin symptoms (*e.g.,* pruritus, urticaria) but do not treat respiratory or cardiovascular symptoms. Nonsedating antihistamines may be used as adjunctive, after epinephrine is used for anaphylaxis.[17] Other adjunctive treatments that may be considered after epinephrine include inhaled bronchodilators, supplemental oxygen, and intravenous fluids.[17] Most allergic reactions for food allergy are mild and do not constitute anaphylaxis. In these situations, antihistamines may be considered for treatment of mild allergic reactions when using a shared decision-making model.[19]

Another reason for having more than one EAI is that misuse of devices has been reported, so having multiple devices assures that medication will be available to treat an allergic reaction. Data from the U.S. Food and Drug Administration postmarketing surveillance program (MedWatch) showed that 40% of the 105 unintentional injections reported were because the "person was trying to inject self or another person having an allergic reaction"[20] and another 13% resulted when the "person was trying to inspect, familiarize himself/herself with, or was holding, an epinephrine auto-injector when it 'accidentally fired'."[20]

WHEN SHOULD EAIs BE USED?

The practice parameter recommends that counseling for patients at high risk of anaphylaxis should emphasize the importance of carrying EAIs because allergic reactions are not predictable and should teach patients proper indications and use.[1] Although prescribing EAIs is a necessary step in preparing patients to treat allergic reactions, it is not the only step. Prescriptions are not always filled,[21] and, even when the prescription is filled, patients do not consistently carry their EAIs.[21,22] Analysis of data also shows that severe allergic reactions are not always treated with epinephrine, in part because EAIs were not available at the time of reaction.[23] Furthermore, reactions are not treated even when the EAIs are available.[24] Studies that examined reasons for not using EAIs to treat severe reactions noted that often patients and/or families reported not recognizing the signs and symptoms that warranted epinephrine.[23,25]

Written emergency action plans can serve as an educational tool to help patients recognize signs and symptoms of severe reactions that would warrant use of EAIs.[19] A survey of caregivers of young children with a history of food allergic reactions found that, although there was no difference in the number of organ systems involved in the severe allergic reaction, those who had been provided a written action plan used their EAI more often to treat the allergic reactions.[26]

In addition to when to use the EAI, education on how to use the EAI is important. Demonstration with a trainer is associated with a higher likelihood of being able to correctly trigger the device.[27] EAI competency does decline over time,[28] and the time since the last training is an important parameter that affects the ability to use the device correctly.[29] Therefore, the practice parameter recommends teaching EAI use with a trainer device on a regular basis.[1]

It is also important to consider the health literacy of the patient and/or family when providing education. In a survey of caregivers of children with food allergy from an urban allergy clinic, health literacy was assessed by using the Newest Vital Sign, a validated index with six questions related to the ability to read

an ice cream label. Lower caregiver health literacy was associated with fewer correct steps for using the EAI, a higher rate of failure to carry the EAI at the visit, higher rate of food allergy reactions in the past 12 months, and more knowledge gaps in the treatment of allergic reactions (as assessed by clinical vignettes).[30] Strategies that can be used for effective education include assessing baseline understanding, using plain language and visual aids, and using teach back to confirm patient understanding.[31]

FUTURE TRENDS

A number of barriers to using EAIs have been identified and range from gaps in recognizing signs and symptoms of anaphylaxis to patient concerns about EAIs.[25] Continued research is needed to develop and validate biomarkers to identify patients at higher risk for anaphylaxis and create algorithms to guide decision-making about managing allergic reactions (when to use epinephrine, when to opt for home management versus activate EMS). Work is also needed to develop educational tools for patients, caregivers, and community members on recognizing signs and symptoms of severe reactions and the role of epinephrine for treatment of anaphylaxis. Alternative delivery routes for epinephrine (*e.g.*, sublingual, intranasal) are actively being studied; U.S. Food and Drug Administration approval of noninjectable epinephrine devices will likely address barriers related to carrying epinephrine and concerns about needles.[32]

CONCLUSION

Ready access to epinephrine *via* EAIs allows patients to self-manage allergic reactions. This is an important resource for patients at risk for anaphylaxis because allergen exposures can occur accidentally and reaction severity is unpredictable. Assessing the need for EAIs is essential because not every patient who has a diagnosis of immunoglobulin E–mediated allergy necessarily has a high risk for anaphylaxis. Decisions with regard to the number of EAI devices to prescribe as well as to carry on a regular basis will depend on patient-specific as well as allergen-specific factors. Along with a prescription, education is necessary for patients to understand how to use the EAI device and recognize signs and symptoms that would warrant epinephrine treatment. Shared decision-making will also guide choices as to when home management of anaphylaxis is appropriate versus immediate activation of EMS after the EAI is used.

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