

Acute At-Home Management of Anaphylaxis: 911: What Is the Emergency?



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The appropriate at-home management of anaphylaxis begins with patient education on recognition and treatment, especially when and how to use epinephrine. Delayed administration of epinephrine as well as having severe symptoms and needing multiple doses of epinephrine to treat symptoms are risk factors for biphasic anaphylaxis. The successful implementation of at-home management of anaphylaxis requires appropriate patient selection and an algorithmic approach that recommends activation of emergency medical services (EMS) when the patient does not adequately respond to at-home administration of epinephrine or there are extenuating patient-related circumstances. Fortunately, approximately 98% of anaphylactic episodes respond to 2 or fewer doses of epinephrine, the standard prescription used for epinephrine autoinjectors; fatal anaphylaxis is very rare, as low as 0.002 deaths/million person-years; and biphasic reactions are uncommon (~5%), and only extremely rarely lethal. Thus, most common concerns leading to recommended EMS activation and emergency department visits after epinephrine administration are generally unsubstantiated. Furthermore, emergency department visits do not always lead to better treatment and drive health care costs higher. Open communications with patients and families regarding risks and benefits of at-home management and observation versus EMS activation and emergency department evaluation after epinephrine administration for anaphylaxis are essential. However, we believe the data indicate that it is time to reconsider the often used and taught approach that recommends EMS activation whenever epinephrine is used. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2274-9)

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In November 2020, we published an article in this journal that addressed how patients might manage an anaphylactic event without activating emergency medical services (EMS).¹ At the time, hospitals were overrun with coronavirus disease (COVID) cases, and there were no available vaccines or treatments. Accordingly, we suggested that in appropriate patients, self-management of anaphylaxis did not always require activation of EMS, which would ultimately lead to an emergency department (ED) visit and potential exposure to patients infected with COVID. Since that time, vaccines against COVID and other treatments have been made available, and the pandemic continues, but is waning. In this rostrum, we examine the possibility of home management of anaphylactic events, even in times without a pandemic. This opinion goes against common teachings of the past, which dictated that any patient who had to inject epinephrine to treat a potential anaphylactic event needed to activate EMS and/or go to a hospital ED.

The appropriate management of an anaphylactic event is immediate treatment with epinephrine.² The quicker the treatment, the less likely a patient is to develop serious consequences of an anaphylactic event (Table 1). In telling patients that they must activate EMS after injecting epinephrine, we may be inadvertently causing patients to delay the administration of epinephrine. The anxiety, fear, and expense of activating the EMS may make patients hesitant to use epinephrine.

We propose that if patients are appropriately selected, educated, and armed with the correct medications for self-management, treatment of an anaphylactic event using a home management algorithm should decrease the necessity of an ED visit and improve the outcomes of an anaphylactic event due to more prompt administration of epinephrine. Although potentially serious, up to 80% of anaphylaxis events either spontaneously resolve or require minimal treatment.⁴ It is estimated that

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and Immunology; and is reviewer for UpToDate. A. Nowak-Wegrzyn receives research support from Alladapt Immunotherapeutics and Regeneron; reports speaking fees from Nestle, Danone, and Thermofisher; reports royalties from UpToDate; serves as an Associate Editor for the *Annals of Allergy, Asthma and Immunology*, chair of the American Board of Allergy and Immunology Board of Directors, director of the American Academy of Allergy Asthma and Immunology Board, and the chair of the Medical Advisory Board of the International Food protein-induced enterocolitis syndrome Association.

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Abbreviations used

COVID-coronavirus disease

EAI-epinephrine autoinjector

ED-emergency department

EMS-emergency medical services

OR-odds ratio

only 10% of reactions have a suboptimal response to a first dose of epinephrine and only 2% to 3% are treated with more than 2 doses of epinephrine. Thus, more than 95% of patients who have the recommended minimum of 2 doses of self-injectable epinephrine available should be able to appropriately manage anaphylaxis themselves. Indeed, fatal anaphylaxis is very rare, with an incidence ranging from 0.5 to 1 death per million person-years. In a recent publication, the range of anaphylaxis mortality rate for all causes was 0.002 to 2.51 deaths per million person-years.⁵ This rate is much less than the risk of accidental death or death from COVID in the general population and is roughly equivalent to the incidence of death due to lightning.⁶

It is also important to recognize that activation of EMS does not guarantee better outcomes. As noted above, better outcomes are dictated by more timely administration of epinephrine for anaphylaxis. In the United States, the emergency response time for an ambulance is approximately 7 minutes and this is double in rural settings, with nearly 1 in 10 encounters waiting up to 30 minutes.⁷ By then, most anaphylactic events would either respond to epinephrine administered at home or resolve spontaneously. Even in the best of circumstances, it can be a significant amount of time before a patient is transported to and evaluated at an ED. Once in an ED, the appropriate management needs to be instituted and unfortunately, this does not always occur as discussed below.

The most common concerns that have led to recommended ED visits after an anaphylactic event are not often justified and lead to considerable health economic cost. Given that 98% of anaphylactic reactions respond to 2 or fewer doses of epinephrine, fatal reactions are very rare, and the feared biphasic reactions are uncommon and very rarely lethal.^{2,8,9} We believe that self-management using an alternative algorithm (Figure 1) with the appropriate patients¹ should be the new normal even when there is no or significantly less fear of exposure to a virulent pathogen such as COVID.

Appropriate patients for home self-management should have the following characteristics: be capable and adherent or have immediate access to a caregiver/individual who is capable to appropriately assist; immediate access to a minimum of 2 doses of epinephrine; have a clear understanding of the risk/benefit of self-management; and have a person or persons immediately available to provide help if needed.¹ The recommendations herein apply only to in-home management and do not apply to school, daycare, restaurant, or work environments (Table II).

Below, we provide further detail by addressing what typically occurs in an ED visit for anaphylaxis, highlighting the risk factors for severe, biphasic, and fatal reactions, and the economic impact of an ED visit. We provide this information to help the clinician and patient arrive at a personalized approach with shared decision

making that considers the potential upsides and downsides of anaphylaxis self-management without activation of EMS.

RISK FACTORS FOR SEVERE ANAPHYLAXIS

The true prevalence of severe anaphylaxis reactions is uncertain because there is lack of a universally accepted grading system. A multidisciplinary group recently developed a severity grading system for acute allergic reactions to standardize research outcomes and communication among providers, patients, and families.¹⁰ This grading system is applicable for all ages (infants-adults), accounts for subjective symptoms, and is independent of treatment given. Prospective validation is needed.

Thus far, studies have used various surrogate markers to identify severe anaphylaxis, such as use of multiple epinephrine doses for treatment and hospital admission, because these are clearly defined features. However, these remain imperfect study outcome measures because determination of treatment and hospitalization can be influenced by local approaches to anaphylaxis management (ie, geographic variations in rates of epinephrine use for anaphylaxis),¹¹ institutional policies and procedures (ie, epinephrine treatment triggers automatic admission at some hospitals), and patient/family factors.

Several risk factors have been associated with severe anaphylaxis. These include age 65 years or more, male sex, cardiac or pulmonary comorbidities, and mastocytosis.¹² Medications, insect venom, and iatrogenic triggers are more often identified in severe cases of anaphylaxis.¹³ A previous ED visit or hospitalization for anaphylaxis, use of beta blockers or angiotensin-converting enzyme inhibitors in proximity to allergen exposure, and vigorous physical activity are additional patient factors that have been found to have associations with increased severity of anaphylaxis.^{12,14} Comorbid asthma has been examined, with several studies demonstrating an association between asthma and severity of food allergy reaction,^{15,16} but an analysis of the European Anaphylaxis registry found an inverse association.¹² A recent study found that individual patients experience reproducibly stereotypic anaphylactic reactions over time, which are unique to a given patient, irrespective of the cause of anaphylaxis, including foods, medications, mast cell disorders, and idiopathic anaphylaxis. In contrast, symptom sequences during anaphylaxis were found to not be reproducible between individuals.¹⁷ Patients with the above-listed risk factors and those with a history of severe anaphylaxis episodes should not consider the algorithmic approach for self-management without appropriate consultation with their physician.

Although most anaphylaxis episodes resolve after a single dose of epinephrine, some do require multiple doses. A meta-analysis that included 86 studies and more than 36,000 anaphylaxis events found that 7.7% (95% CI, 6.4-9.1) of anaphylaxis cases from any trigger were treated with more than 1 dose of epinephrine and 2.2% (95% CI, 1.1-4.1) were treated with 3 or more doses.¹⁸ One study of 3498 anaphylaxis cases across 9 EDs in Canada reported that epinephrine before arrival to the ED was associated with decreased likelihood of receiving multiple epinephrine doses in the ED, leading to the conclusion that delayed treatment with epinephrine is a risk factor for increased epinephrine requirement to control anaphylaxis symptoms.¹⁹ Delayed treatment with epinephrine was also noted to be a risk factor for hospitalization in a study of pediatric food-induced anaphylaxis cases that presented to the ED and received epinephrine.²⁰

TABLE 1. Considerations for early epinephrine treatment in anaphylaxis³

Benefits
- Decreased risk of: - needing additional doses of epinephrine - biphasic anaphylaxis - hospitalization - fatality
Mechanism of action
<i>Alpha-adrenergic stimulation:</i> - increased vascular smooth muscle contraction (vasoconstriction) - pupillary dilator muscle contraction (mydriasis) - intestinal sphincter muscle contraction - decreased edema
<i>Beta-adrenergic stimulation:</i>
Beta-1 receptors - increased heart rate - increased myocardial contractility - renin release
Beta-2 receptors - bronchodilation - dose-dependent inhibition of mast cell degranulation - vasodilation - tocolysis - increased aqueous humor production

RISK FACTORS FOR BIPHASIC REACTIONS

Biphasic anaphylaxis is defined as being highly likely when all of the following 4 criteria are fulfilled:

1. New/recurrent symptoms/examination findings must fulfill the 2006 National Institute of allergy and infectious diseases/Food Allergy & Anaphylaxis Network anaphylaxis criteria.²¹
2. Initial symptoms/examination findings must completely resolve before the onset of new/recurrent symptoms/examination findings.
3. There cannot be repeat allergen exposure before the onset of new/recurrent symptoms/examination findings.
4. New/recurrent symptoms/examination findings must occur within 1 to 48 hours from complete resolution of initial symptoms/examination findings.²²

Based on a recent meta-analysis, the pooled estimate of biphasic reactions among all anaphylaxis cases was 3.92% (95% CI, 2.88-5.32).²³

The 2020 practice parameter on anaphylaxis examined risk factors for biphasic anaphylaxis.² Based on very low certainty of evidence, factors associated with biphasic anaphylaxis include more severe initial presentation of anaphylaxis (odds ratio [OR], 2.11; 95% CI, 1.23-3.61) or more than 1 dose of epinephrine required to treat the initial symptoms (OR, 4.82; 95% CI, 2.70-8.58). Other risk factors for biphasic anaphylaxis include wide pulse pressure (OR, 2.11; 95% CI, 1.32-3.37), unknown anaphylaxis trigger (OR, 1.63; 95% CI, 1.14-2.33), dermatologic signs and symptoms (OR, 2.54; 95% CI, 1.25-5.15), and drug as the culprit allergen in children (OR, 2.35; 95% CI, 1.16-4.76). The more recent meta-analysis identified that delayed treatment with epinephrine was also a risk factor for biphasic reactions.^{19,23} This study found that first epinephrine dose in ED and delay of 30 minutes between symptom onset and epinephrine dose were associated with biphasic reactions (OR, 3.72 and 3.39, respectively).

RISK FACTORS FOR FATAL ANAPHYLAXIS

Fatalities due to anaphylaxis are fortunately a very rare occurrence. Population fatality rates range from 0.47 to 0.69 per million persons, and hospital (ED and inpatient) fatality rates range between 0.25% and 0.33%.²⁴ Rates differ by allergen, with food being the least common allergen implicated in fatal anaphylaxis.⁴ Risk factors may differ by allergen: underlying cardiovascular disease and older age (age >65 years) for drug-induced fatalities, delayed epinephrine administration for food-induced fatalities, and cardiovascular disease or mastocytosis for insect sting fatalities.⁶ Teenagers and young adults are over-represented in food-induced fatalities^{16,25,26}; this is most likely due to risk-taking behavior with avoidance and lack of/poor epinephrine availability.

WHAT GOES ON IN THE ED?

Even though multiple guidelines recommend that epinephrine is first-line therapy in the treatment of anaphylaxis, with anti-histamine and steroids suggested as second-line/supportive therapy, as well as studies demonstrating that delayed epinephrine administration is a risk factor for morbidity and mortality in anaphylaxis, multiple publications show low utilization of epinephrine both at home and in the ED setting.^{27,28} This is exemplified by a recent analysis that examined the use of epinephrine before ED arrival, demonstrated that only 36.3% of patients used an epinephrine autoinjector (EAI) before presentation to the ED or urgent care center.^{6,29} Reasons for lack of use of EAI before acute care intervention include never actually filling the prescription, lack of carriage, fear of a needle, and concern about having to go to the emergency room after use of the EAI. Sadly, once admitted to the ED, numerous studies reveal that patients often do not receive epinephrine despite the fact that this would likely be a beneficial intervention. This is illustrated in a study by Gaeta et al,³⁰ who examined US ED visits for acute allergic reactions between 1993 and 2004, demonstrating that although 63% of 12.4 million allergy-related visits were coded as urgent, including 4% requiring hospitalization, only 7% of these patients were actually given epinephrine.³⁰ Furthermore, in the subset with the most severe reaction, although 63% received an antihistamine, 61% a corticosteroid, and 38% an H₂ blocker, only 50% received epinephrine. Overall, these findings highlight that ED physicians often rely on second-line agents for the treatment of significant allergic reactions, despite robust data as well as national and international guidelines stressing the importance of early use of EAI. It should also be noted that following admission to the ED, even when epinephrine is used, most patients are discharged after only a few hours, in most cases with minimal added medical intervention. The most recent ED practice parameter for anaphylaxis states that clinicians should “strongly consider observing patients who have experienced anaphylaxis for at least 4 to 8 hours and observe patients with a history of risk factors for severe anaphylaxis for a longer period,” including asthma, previous biphasic or protracted anaphylaxis, repeat doses of epinephrine, wheezing, hypotension, or pharyngeal edema.^{31,32} Recent publications suggest that this wait time can be further stratified on the basis of severity of symptoms at presentation to the ED as well as potential risk factors, suggesting a 3- to 4-hour wait time for those who are asymptomatic shortly after administration of epinephrine with no other risk factors, a 6- to 8-hour wait time for patients with a

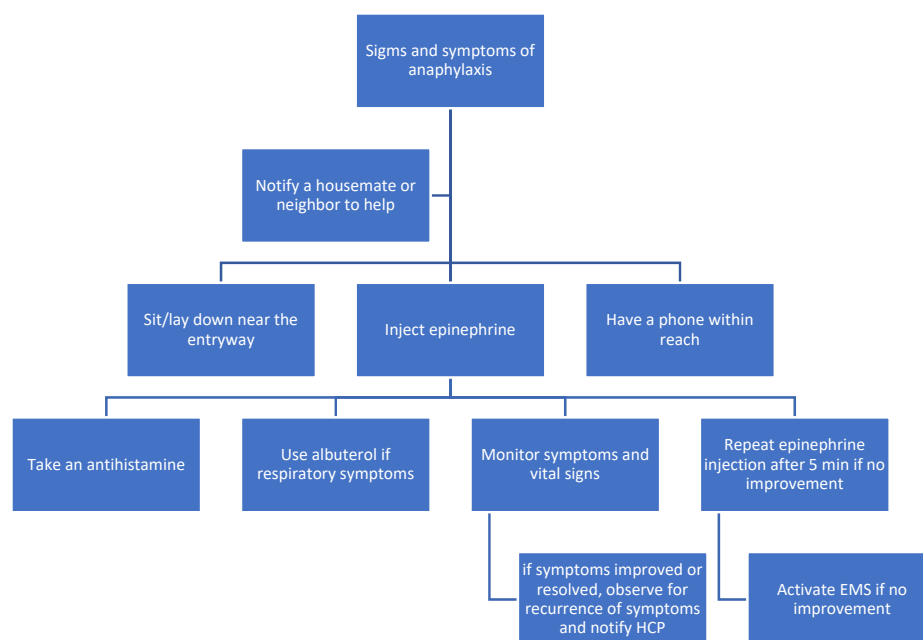


FIGURE 1. Algorithmic approach for at-home anaphylaxis management. *HCP*, Health care provider.

TABLE II. Considerations for home management of anaphylaxis

Home management can be considered if:	Home management should not be considered if:
• Patients/caregivers engaged in shared decision process • Immediate access to at least 2 EAI • Immediate access to person(s) who can provide help if needed • Clear understanding of the symptoms warranting the immediate use of EAI, availability of the anaphylaxis treatment plan • Familiarity with the EAI device administration technique • Clear understanding of the benefits of early epinephrine treatment in anaphylaxis • Good adherence to previous treatment recommendations, eg, use EAI for anaphylaxis in the past and use of controller medications for chronic conditions	• Patients/caregivers not comfortable with managing anaphylaxis without activating EMS/ED • No availability of EAIs or only 1 EAI • Being alone, without immediate access to person(s) who can provide help if needed • Being unaware of the allergic symptoms that warrant the use of EAI • Lack of technical proficiency with administration of EAI • Hesitance about the intramuscular injection (needle phobia) • Concerns about the potential epinephrine side effects • Past history of severe/near-fatal anaphylaxis treated with more than 2 doses of epinephrine, hospitalization, intubation • Poor adherence to previous treatment recommendations, eg, not administering EAI for anaphylaxis in the past and not using controller medications for chronic conditions

history of asthma, mild wheezing on presentation, and/or slowly resolving symptoms, and hospitalization for patients with a history of prior protracted or biphasic anaphylaxis, 2 or more doses of epinephrine administered, moderate to severe wheezing on presentation, hypotension, pharyngeal edema, and persistence of worsening of symptoms.³³ Furthermore, the 2020 Anaphylaxis PP states that “for patients without severe risk features [for biphasic reaction], discharge after a 1-hour asymptomatic observation may be reasonable.”² Interestingly, there are presently no studies that have examined whether early EMS (EMS) utilization actually reduces fatality from anaphylaxis.^{34,35}

EPINEPHRINE SIDE EFFECTS

As noted earlier, despite multiple guidelines recommending the use of epinephrine as the first and primary treatment for an anaphylactic event, both patients and physicians are often

reluctant to use this lifesaving drug. Some of the factors associated with this reluctance are described earlier. Another key factor involved in avoiding epinephrine use is the perceived and real side-effect profile of this drug (Table III). Of the listed potential adverse consequences of epinephrine use, those involving the cardiovascular system are viewed as the most important.³⁷ Cardiovascular side effects have included elevations in heart rate and/or blood pressure. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. However, these side effects are extremely rare at the doses used with EAI and do not consider the potential benefit of using epinephrine to abort a severe anaphylactic reaction that could result in serious medical consequences including death. Thus, the authors as well as guideline parameters recommend epinephrine

TABLE III. Putative side effects reported for epinephrine (see Lieberman et al³⁶)

• abnormal or decreased touch sensation
• arm, back, or jaw pain
• bleeding, blistering, burning, coldness, discoloration of the skin, feeling of pressure, hives, infection, inflammation, itching, lumps, numbness, pain, rash, redness, scarring, soreness, stinging, swelling, tenderness, tingling, ulceration, or warmth at the injection site
• blurred vision
• chest pain or discomfort
• chest tightness or heaviness
• dizziness
• fainting
• fast, irregular, pounding, or racing heartbeat or pulse
• fear or nervousness
• headache
• nausea or vomiting
• paleness of the skin
• pounding in the ears
• restlessness
• shakiness in the legs, arms, hands, or feet
• shortness of breath
• slow or fast heartbeat
• stroke
• sweating
• trembling or shaking of the hands or feet
• troubled breathing
• unusual tiredness or weakness
• injecting the needle into the thumb
• subendocardial necrosis

as the immediate drug of choice to treat anaphylaxis without any absolute contraindications.

ECONOMIC CONSIDERATIONS

Very limited data are available to compare the costs incurred with the immediate activation of the EMS and evaluation in the ED following EAI administration at home compared with watchful waiting.

Two studies provided estimates of direct medical costs for food allergy, including emergency services.^{35,38} In a cross-sectional survey conducted from November 28, 2011, through January 26, 2012, based on a representative sample of 1643 US caregivers of a child with a current food allergy, direct medical costs were estimated at \$4.3 (95% CI, \$2.8-\$6.3) billion annually, including clinician visits, ED visits, and hospitalizations. In 2007, based on data from federal databases by using *International Classification of Diseases, Ninth Revision* codes, the direct medical costs of food allergy and food-induced anaphylaxis were \$225 million, and indirect costs were \$115 million. Office visits accounted for 52.5% of costs, emergency visits 20%, inpatient hospitalizations 11.8%, outpatient visits 3.9%, ambulance runs 3%, and epinephrine devices 8.7%.³⁸

Only 1 study to date has used a Markov model simulation to investigate the cost-effectiveness of a routine recommendation advising patients to activate EMS defined by calling 911 for ambulance transport and undergoing subsequent ED evaluation, after home epinephrine use in peanut-allergic children.³⁵ Markov modeling was applied to compare outcomes of peanut-allergic

children randomized to immediate activation of EMS despite improvements or to EMS activation only if symptoms of anaphylaxis did not immediately improve following EAI injection at home. The model made a number of assumptions on the basis of published data such as the risk of fatality (5.77×10^{-7}), cost of emergency services (ED visit \$660.72; EMS \$562.00), and the probability of favorable response to treatment with 1 dose of epinephrine at home of 88%. Because the risk reduction associated with early EMS use after prehospital epinephrine administration is unknown, a 10-fold increase in peanut allergy fatality was arbitrarily chosen as the base-case comparison (with sensitivity analyses applied to 100-fold and 1000-fold increase in risk), as well as modeled EMS activation of parent transport of the child without an ambulance to the ED. Cost-effective care was defined as less than \$100,000 per life year saved. They found that the fatality risk associated with early EMS use was minimal, with a per-patient fatality rate over a 20-year horizon of 1.2×10^{-6} versus 1.9×10^{-6} for a wait and see approach. The incremental cost per life year saved was \$142,943,447 for early EMS versus wait and see, with the cost per death prevented reaching \$1,349,335,65 as the simulation concluded over 20 years. Cost of early EMS activation rose to \$321,625,534 per life year saved (\$3,035,454,848 per death prevented) if a 5-fold increase in fatality risk was assumed and was \$12,997,173 per life year saved (\$122,689,936 per death prevented) if a 100-fold increase in fatality risk was assumed. The authors concluded that medical observation of a treated and promptly resolved peanut-allergic reaction in children has minimal benefits and excessive costs. This model is limited by a multitude of assumptions, and it may not be applicable to food allergy other than peanut and to food-allergic adults, who appear to have a higher rate of treatment with 2 or more epinephrine doses.

CONCLUSIONS

Most common concerns leading to ED visits after epinephrine administration for potential anaphylaxis are generally unsubstantiated. Ninety-eight percent of reactions respond to 2 or fewer doses of epinephrine, which is the standard prescription used for EAIs. Fatal anaphylaxis is very rare, as low as 0.002 deaths/million person-years. Biphasic reactions are uncommon ($\sim 5\%$), not lethal (except in exceptionally rare case reports), and delayed beyond traditional ED observation times (median, 11 hours). The economics of EMS activation and a subsequent ED visit are high, and the provided treatment and observation periods are often not appropriate to manage an acute event or monitor for a biphasic reaction. Nonetheless, the implementation of at-home management of anaphylaxis requires appropriate selection and education of patients, access to epinephrine, and an algorithmic approach that recommends activation of EMS when the patient does not adequately respond to at-home administration of epinephrine or there are extenuating patient-related circumstances. As reviewed by Dribin et al,³⁹ research exploring risk factors for future anaphylaxis, the appropriate use of epinephrine, and follow-up care postanaphylaxis is needed. Furthermore, this approach should only be implemented with shared decision making of patients, caregivers, and health care providers. Overall, the data indicate that it is time to reconsider the often used and taught approach that recommends EMS activation whenever epinephrine is used.

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