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Prevention of anaphylaxis: the role of the epinephrine auto-injector

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ABSTRACT

Anaphylaxis is a life-threatening condition, with at-risk individuals remaining at chronic high risk of recurrence. Anaphylaxis is frequently underrecognized and undertreated by healthcare providers. The first-line pharmacologic intervention for anaphylaxis is epinephrine, and guidelines uniformly agree that its prompt administration is vital to prevent progression, improve patient outcomes, and reduce hospitalizations and fatalities. Importantly, healthcare costs potentially associated with failure to provide epinephrine (hospitalizations and emergency department visits) generally exceed those of its provision. At-risk patients are prescribed epinephrine auto-injectors to facilitate timely administration in the event of an anaphylactic episode. Despite guideline recommendations that patients carry two auto-injectors at all times, a significant proportion of patients fail to do so, with cost of medicine cited as one reason for this lack of adherence. With the rise of high-deductible healthcare plans, patient adherence to recommendations may be further impacted by increased cost sharing. The recognition and classification of epinephrine as a preventive medicine by both the US Preventive Services Task Force and insurers could increase patient access, improve outcomes, and save lives.

HIGHLIGHTS

- Timely epinephrine injection prevents anaphylaxis-related hospitalization or death.
- At-risk patients should carry two epinephrine auto-injectors, but many do not.
- Prescription abandonment rates increase with higher out-of-pocket costs.
- Limited or no cost sharing is required for preventive medications.
- Classifying epinephrine auto-injectors as preventive would improve outcomes.

INTRODUCTION

Allergies are the sixth leading cause of chronic illness in the United States, affecting more than 50 million Americans, and costing the healthcare system more than \$18 billion annually.¹ Individuals in hyperallergic states are at chronic high risk for the occurrence of acute anaphylactic episodes, and as many as 49 million individuals are thought to be at risk in the United States.² Annual direct costs of anaphylaxis are estimated at \$1.2 billion.² Anaphylactic episodes are serious, multi-system, life-threatening, and generalized or systemic hypersensitive or allergic reactions, which are rapid in onset and potentially fatal.³⁻⁵ Anaphylaxis may be either immunologic (immunoglobulin E [IgE]-mediated or non-IgE-mediated) or nonimmunologic; both forms are referred to as “anaphylaxis” in this review, in line with international guidelines and consensus statements.³ Risk factors for anaphylaxis include age,^{5,6} comorbidities (eg, asthma⁷), and certain medications (eg, beta blockers and angiotensin-converting enzyme inhibitors).^{5,6}

Anaphylaxis occurs on a continuum and can begin with relatively minor symptoms before progressing, in an unpredictable manner, to a life-threatening condition.³ The most common signs and symptoms include changes in the skin (such as itching, erythema, pruritus, urticaria, angioedema) and respiration (including bronchospasm, laryngeal edema, cough, respiratory arrest); effects on the gastrointestinal, cardiovascular, and central nervous systems may also be evident.^{3,5} Anaphylaxis is often underrecognized by healthcare professionals both in general practice and in emergency care,⁶ particularly if cutaneous signs and symptoms are not present (these are absent in 10-20% of patients).⁵

International guidelines concur that anaphylaxis is a medical emergency and requires rapid intervention.^{5, 6} Prompt treatment with epinephrine, the only first-line intervention for anaphylaxis, is recommended to prevent the progression of an anaphylactic episode.^{4-6, 8} For patients experiencing an anaphylactic event, epinephrine is the only medication proven to prevent hospitalization and fatalities.⁶ Because the onset of anaphylaxis symptoms often occurs in the community setting,³ at-risk patients should be prescribed epinephrine auto-injectors to provide rapid intramuscular administration of epinephrine.^{4, 7, 9} However, a large number of patients prescribed epinephrine auto-injectors do not have access to one at the time of an allergen exposure, leading to delayed medication administration and increased risk of progression to severe anaphylaxis.¹⁰⁻¹³

Currently, many high-deductible healthcare plans include epinephrine auto-injectors among those medications to which the plan's deductible applies rather than as a preventive medicine exempt from cost sharing. Because high deductibles and high cost sharing, such as those in high-deductible healthcare plans, may lead to decreased use of medical care,¹⁴⁻¹⁷ the recognition and classification of epinephrine as a preventive medicine could improve patient access. Recommended preventive services or medications (ie, those graded A or B by the US Preventive Services Task Force [USPSTF]) are not subject to any cost sharing requirements for the patient, (eg, deductibles, copayments) (as discussed below), as per the Patient Protection and Affordable Care Act 2010.¹⁸ Here, the role of epinephrine auto-injectors in the prevention of anaphylaxis progression and their potential classification as preventive by the USPSTF and inclusion on healthcare plan preventive medication lists are reviewed.

ECONOMIC BURDEN OF ANAPHYLAXIS

The reported incidence of anaphylaxis in the United States is 49.8 in 100,000 person-years,¹⁹ with a lifetime prevalence of approximately 1.6-5.1%.¹⁰ Anaphylaxis represents an increasing burden on emergency departments and hospitals. One study reported a 2.23% annual increase in anaphylaxis-related hospitalizations from 1999-2009, reaching 25.1 per million population annually.²⁰ The same authors calculated that, from 2006-2009, the number of anaphylaxis-related emergency department presentations without hospital admission ranged from 17,735-21,822.²⁰ From 1999-2009, anaphylaxis-related deaths totaled 2229 (0.69 per million population), with the annual number of deaths ranging from 186-225, (0.63-0.76 per million population).²⁰ However, healthcare providers frequently underreport anaphylaxis because of the unexpected nature of the event, a lack of accurate diagnosis, and a lack of accurate diagnostic coding.^{4, 21, 22} This means that currently reported rates of anaphylaxis prevalence and associated mortality are likely to be underestimates. In addition, inaccurate coding makes it difficult for payers to accurately determine the costs of treating anaphylaxis versus the costs associated with preventive measures.²²

Of the estimated annual direct anaphylaxis costs of \$1.2 billion, \$294 million relates to epinephrine costs. Indirect expenditures are estimated at \$609 million.² A survey of caregivers of children with a food allergy estimated direct medical costs (including emergency department visits and hospitalizations) to be higher, at \$3.7 billion per year.²³ In a review of literature and healthcare databases, epinephrine costs amounted to less than 9% of the total direct costs of treating patients with food allergy and anaphylaxis, while emergency department visits accounted for 20% of direct costs.²⁴

IMPORTANCE OF PROMPT TREATMENT OF ANAPHYLAXIS

Guidelines and consensus statements emphasize the importance of prompt initial administration of epinephrine for the treatment of anaphylaxis.³⁻⁸ Some authors have specified that epinephrine is indicated in patients with “impending anaphylaxis”²⁵ or should be administered “sooner rather than later.”²⁶ Members of the Anaphylaxis Practice Parameter Workgroup, commissioned by the Joint Task Force on Practice Parameters, recommend immediate treatment with epinephrine to prevent symptom progression and the occurrence of more severe anaphylaxis.⁷

Delayed epinephrine administration leads to worse outcomes and fatalities.^{3, 8, 27} A UK study found that of all anaphylaxis fatalities occurring in a 6-year period, only 14% of the victims had received epinephrine before cardiac arrest.¹² In a 14-month US study of fatal or near-fatal food-induced anaphylaxis in children/adolescents, only 33% of the patients with a fatal reaction received epinephrine within an hour of allergen exposure, while none of the near-fatal–reaction patients received epinephrine at the first sign of symptoms.²⁸ Although 50% of the patients with a fatal reaction had been previously prescribed epinephrine auto-injectors, none had them available at the time of the reaction. In addition to the risk of fatality, failure to promptly administer epinephrine may increase the likelihood of biphasic anaphylaxis, in which symptoms recur 1-72 hours (typically within 8-10 hours) after resolution of the initial symptoms.⁵

INADEQUATE TREATMENT OF ANAPHYLAXIS

Despite clear recommendations for prompt epinephrine administration, recognition of anaphylaxis is often inconsistent and many patients receive inadequate management. A review of a national database demonstrated that 57% of

anaphylactic episodes are not recognized in the emergency department,²⁹ while another study reports that anaphylaxis is underrecognized in both emergency departments and urgent care centers.³⁰ Overall, this lack of recognition and management of anaphylaxis means that patients often do not receive first-line epinephrine treatment. For example, in a study of pediatric patients with food-induced anaphylaxis, only 61% received epinephrine (either pre or post admission). The median length of emergency department stay was shorter for those patients who received epinephrine prior to admission to the emergency department (3 hours vs 4 hours, $P = 0.03$), and these patients were also less likely to be hospitalized (17 vs 43%, $P < 0.001$).²⁷ Similarly, other studies in pediatric patients have shown that as few as 33-50% of anaphylactic patients admitted to the emergency department receive epinephrine.^{31, 32} In a 12-year study of 12.4 million emergency department visits for allergic reactions and anaphylaxis, only 50% of patients with the most severe reactions received epinephrine.³³

Instead of receiving first-line epinephrine treatment, patients were often treated with second-line therapies, including antihistamines and glucocorticoids.^{27, 32, 33} However, these medications only treat the cutaneous symptoms of anaphylaxis and do not prevent or relieve life-threatening upper airway obstruction.⁵ Furthermore, they may require several hours to take effect, limiting their utility in the early hours of an anaphylactic episode.⁵

ADHERENCE

Anaphylaxis has a high risk of recurrence (estimated to be 30-43%),³⁴ and long-term preventive measures are a key element of patient care. Discharge from the emergency department represents the transition to long-term management, and

emergency department practitioners play a pivotal role in this step.²⁵ Long-term management approaches initiated at discharge should include patient education,^{4, 7} allergen avoidance,^{4, 7, 26} referral to an allergy specialist,²⁶ and the provision of epinephrine auto-injectors.^{4, 5, 7, 26} Current guidelines recommend that at-risk patients carry two epinephrine auto-injectors at all times (as anaphylactic episodes can be biphasic, necessitating the administration of two doses of epinephrine).^{4, 7, 9} However, many patients do not have access to an auto-injector at the time of recurrence. In one survey, 52% of patients who had previously experienced anaphylaxis had never received a self-injectable epinephrine prescription, and 60% did not have an auto-injector available.¹⁰ Other authors have cited even lower figures, with an observational study reporting that only 9-28% of patients requiring epinephrine auto-injectors carried one with them.³⁵ In a study of 14,677 patients in a large health maintenance organization who had received a prescription for an epinephrine auto-injector, only 11% refilled consistently.¹¹

In a survey of allergists, 38% of those who asked patients if they carried their epinephrine auto-injector indicated that one of the most frequent reasons for patients failing to carry an auto-injector was financial inability to fill the prescription.³⁶ Claims data also suggest that financial considerations may represent a barrier to epinephrine auto-injector use in the United States. For example, abandonment rates of the EpiPen[®] auto-injector increase in relation to patient cost; more than 50% of EpiPen[®] prescriptions are abandoned when patient cost exceeds \$300 (Figure 1).³⁷

EPINEPHRINE AUTO-INJECTOR AS A PREVENTIVE MEDICATION

The US Treasury Department defines medications as preventive “when taken by a person who has developed risk factors for a disease that has not yet manifested

itself or not yet become clinically apparent (ie, asymptomatic) or to prevent the reoccurrence of a disease from which a person has recovered.”³⁸ Recommended practices for prevention, trigger avoidance, and treatment indicate that anaphylaxis is a chronic condition with occasional, potentially severe symptom recurrence.²¹ Patients with allergies have risk factors for anaphylaxis, including a previous allergic reaction, comorbidities such as asthma, and treatment with certain medications.⁷ Furthermore, patients who have recovered from anaphylaxis are at risk for reappearance of symptoms in a future episode.⁷ Preventive anaphylaxis care (ie, filling an epinephrine auto-injector prescription or visiting an allergist/immunologist) in the year before an anaphylactic event has been associated with a lower risk of severe anaphylaxis.³⁹ These data support the classification of epinephrine, the only first-line, life-saving treatment for anaphylaxis, as a preventive medication.

PREVENTIVE MEDICINE AND HIGH-DEDUCTIBLE HEALTHCARE PLANS

The USPSTF is an independent, volunteer expert panel that makes evidence-based recommendations on clinical preventive procedures, services, and therapies.⁴⁰ Recommendations are updated regularly, based on evidence level and cost:benefit ratio,⁴⁰ with services being graded A-D or I accordingly (Table 1).⁴¹ The USPSTF recommends that those services receiving grades A or B should be offered or provided to patients. Grade A services are those where there is a high certainty of substantial net benefit, and Grade B services have either a moderate certainty of moderate or substantial benefit or a high certainty of moderate benefit (Table 1).⁴¹

Per the Patient Protection and Affordable Care Act 2010,¹⁸ the cost of those preventive drugs that are given USPSTF grade A or B ratings are covered in healthcare insurance plans, including in high-deductible healthcare plans. In order to

grade preventive medications, the USPSTF evaluates all available peer-reviewed evidence, often including data from randomized controlled trials. However, in the case of some preventive medications recommended by the USPSTF (eg, folic acid for the prevention of neural tube defects), the evidence base contains only limited numbers of randomized controlled trials, due to the nature of the medication.⁴² In the case of epinephrine, which was introduced prior to the advent of randomized controlled trials,⁵ it would be unethical to assess efficacy in placebo-controlled or comparator randomized controlled trials (ie, it would not be ethical to withhold epinephrine when it is the only first-line medication and the only medication known to prevent fatalities).^{43, 44}

Partial coverage and high copayments are associated with decreased uptake of preventive services and poorer patient outcomes.^{45, 46} Increased patient cost sharing is associated with decreased adherence to medications; for each dollar increase in patient copayments, adherence decreases by 0.4% on average.¹⁴ Therefore, classification of medications as preventive (grades A or B) by the USPSTF and subsequent exemption from deductibles in healthcare plans, including high-deductible healthcare plans, would be expected to increase use. In the case of epinephrine auto-injectors, an increase in the number of patients filling prescriptions should improve access at the time of an anaphylactic episode and avoid delay in epinephrine initiation, thereby reducing hospitalizations, fatalities, and treatment costs.

High-deductible healthcare plan enrollment has increased each year, covering up to 19.7 million individuals in the United States in November 2015.⁴⁷ High-deductible healthcare plans have high annual deductibles and out-of-pocket limits. However,

high patient cost sharing is associated with decreased treatment adherence,¹⁴ delayed presentation,⁴⁸ and adverse outcomes, particularly among low-income patients in high-deductible healthcare plans.¹⁵⁻¹⁷ Insurers offer full coverage of the cost of preventive medications with USPSTF grade A or B ratings, and they have latitude to expand their list of preventive medicines beyond this automatic inclusion, providing that the medication conforms to the Internal Revenue Service (IRS) definition of a preventive medication. For classification as preventive within a high-deductible healthcare plan policy, medications must qualify for reimbursement as part of a health savings account and cannot include those used to treat an existing illness, injury, or condition.⁴⁹ In the absence of a specific, IRS-defined list,³⁸ some high-deductible healthcare plan preventive medication lists can be broad and may include such medications as heart failure and diabetes medications, asthma inhalers, blood-thinning agents, and statins.⁵⁰⁻⁵² Preventive drugs and services have been shown to be cost effective in many cases,⁵³ and employers cite increased productivity and decreased costs among their reasons for providing preventive services coverage in employee healthcare plans.⁵⁴ One survey reported that large employers with health savings account –qualified high-deductible healthcare plans were particularly likely to use a liberal definition of preventive medications, with 57% of high-deductible healthcare plans covering preventive medications at 100% in 2013, up from 46% in 2012.⁵⁵

INCLUSION OF EPINEPHRINE AUTO-INJECTOR IN HEALTHCARE PLANS

The evidence presented here suggests that the risk of epinephrine auto-injector prescription abandonment could be diminished by inclusion of epinephrine auto-injectors in preventive medication lists. A review of high-deductible healthcare plans listed under health exchanges in the Managed Markets Insight and Technology

database showed that EpiPen 2-Pak[®] was classed as a tier 1-2 product in 67% of plans, classed as a tier 3-4 product in 6% of plans, “approved” in 5% of plans, and not reimbursed in 22% of plans (Table 2).⁵⁶ However, examples of epinephrine auto-injectors being listed as preventive medications, exempt from high deductibles, in high-deductible healthcare plans are limited.⁵²

SUMMARY AND CONCLUSIONS

Allergy is an important and prevalent condition in the United States, which puts hyperallergic patients at chronic risk of anaphylaxis. Timely recognition of anaphylactic episodes and prompt administration of first-line epinephrine is integral to prevent symptom progression, hospitalization, and death. But current recognition and treatment of anaphylaxis is inadequate, with epinephrine administration frequently delayed or not given as first-line medication. Guidelines recommend that patients carry two epinephrine auto-injectors; however, a significant proportion of patients fail to do so. Considering the cost of auto-injectors compared to the costs of emergency department visits and hospitalizations associated with failure to treat anaphylaxis appropriately, these findings suggest preventive treatment of anaphylaxis with an epinephrine auto-injector would be cost effective.

Epinephrine auto-injectors are currently included in the deductibles of many healthcare plans, which, coupled with the negative impact of high cost sharing, often decreases patient adherence. With more patients enrolling in high-deductible healthcare plans, fewer of them may be willing or able to obtain epinephrine auto-injectors. However, the classification of epinephrine auto-injectors as a grade A or B preventive medicine by the USPSTF and inclusion on preventive medication lists

could be expected to increase patient access to first-line anaphylaxis treatment, improving outcomes and decreasing fatalities.

ACCEPTED MANUSCRIPT

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Table 1 US Preventive Services Task Force (USPSTF) Grade Definitions.⁴¹

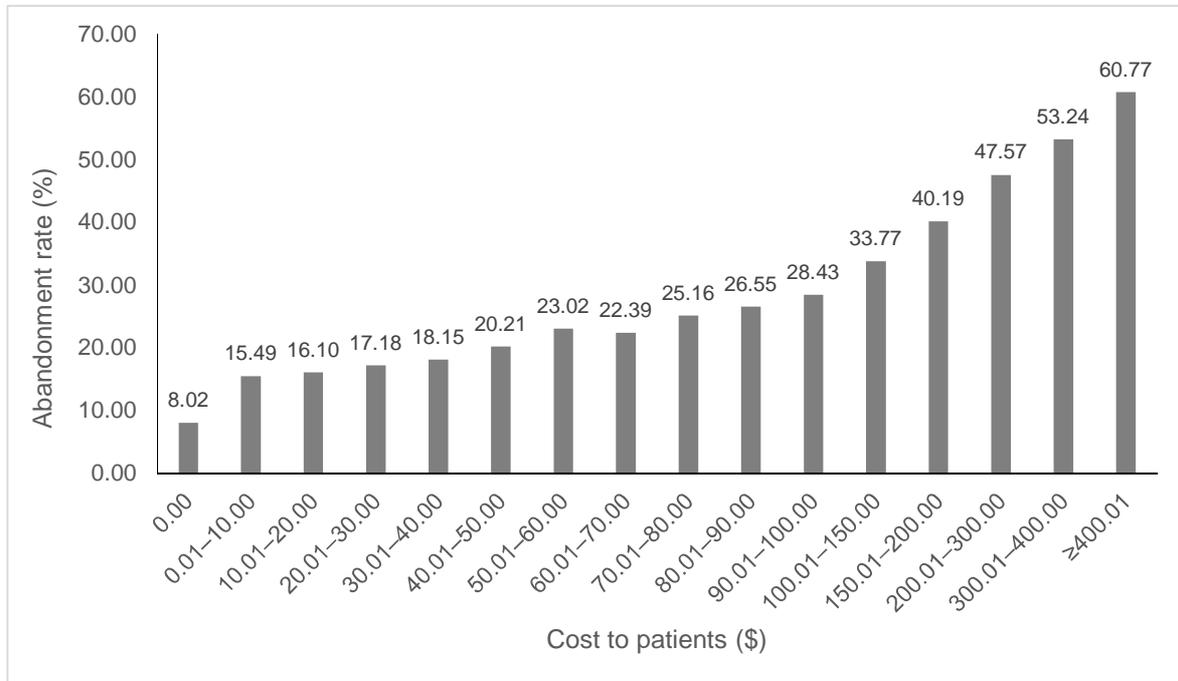
Grade	Definition	Recommendations
A	The USPSTF recommends. High certainty of substantial net benefit.	Offer or provide this service.
B	The USPSTF recommends. High certainty of moderate net benefit or moderate certainty of moderate to substantial net benefit.	Offer or provide this service.
C	The USPSTF recommends selectively offering/providing to individual patients based on professional judgment and patient preferences. Moderate certainty of small net benefit.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against. Moderate or high certainty of no net benefit or that harms outweigh benefits.	Discourage use.
I	THE USPSTF concludes that current evidence is insufficient to assess benefits and harms. Evidence is lacking, of poor quality, or conflicting.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Table 2 High Deductible Health Plan Raw Formulary Status of EpiPen® 2-Pak in Health Exchanges* (N = 100).⁵⁶

Tier 1 (% of plans)	Tier 2 (% of plans)	Tier 3 (% of plans)	Tier 4 (% of plans)	Approved (% of plans)	Not reimbursed (% of plans)
1	66	5	1	5	22

*Numbers are based on a search of the publicly available website www.formularylookup.com. Exchanges contain dynamic information and are updated frequently, so the exact percentages of plans listed here have likely changed since the original search was conducted in July 2015.

Figure 1 Abandonment rates with increasing patient cost of EpiPen® (October 2014-October 2015).³⁷



Clinical significance bullets

- Anaphylaxis is life threatening, underrecognized, and undertreated. Prompt epinephrine administration is integral to preventing hospitalizations and deaths.
- At-risk patients should carry two epinephrine auto-injectors, but many fail to do so.
- Adherence to medications decreases with the increased cost sharing associated with high-deductible healthcare plans.
- Classification of epinephrine auto-injectors as preventive medicines by the US Preventive Services Task Force and/or insurers would eliminate or reduce cost sharing, improving access and outcomes.