
An economic evaluation of prophylactic self-injectable epinephrine to prevent fatalities in children with mild venom anaphylaxis

Marcus S. Shaker, MD

Background: Mild (cutaneous) venom anaphylaxis is the most common presentation of systemic venom hypersensitivity during childhood. Guidelines recommend prophylactic self-injectable epinephrine for children with mild venom anaphylaxis. However, progressive venom-associated reactions are uncommon in this population.

Objective: To characterize the cost-effectiveness of prophylactic self-injectable epinephrine in mild childhood venom anaphylaxis from a societal perspective.

Methods: Cohort simulations were used, and the base case was represented by a 6-year-old child with a history of mild venom-associated anaphylaxis. Long-term survival was modeled using age-adjusted mortality from the 2002 US life tables together with the risk of venom-associated mortality. Model assumptions included market costs of self-injectable epinephrine; the prevalence of venom allergy; US census estimates; venom-associated fatality estimates by the Joint Council of Allergy, Asthma, and Immunology (at least 40 deaths per year); and venom-associated mortality statistics from January 1, 1999, to December 31, 2003, provided by the Centers for Disease Control and Prevention.

Results: The incremental cost of prophylactic self-injectable epinephrine for mild childhood venom anaphylaxis was \$469,459 per year of life saved (\$6,882,470 per death prevented). In sensitivity analyses, the strategy was only cost-effective when the annual venom-associated fatality rate exceeded 2 per 100,000 persons at risk.

Conclusion: Use of prophylactic self-injectable epinephrine to prevent fatalities in children with mild venom anaphylaxis is not cost-effective if the annual venom-associated fatality rate is less than 2 per 100,000 persons at risk.

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INTRODUCTION

Mild (cutaneous) systemic venom-associated anaphylaxis is the most common presentation of venom anaphylaxis during childhood.^{1,2} Such reactions involve urticaria, angioedema, or both distant from the site of an insect sting but with no involvement of other organ systems.³ Guidelines suggest that any child who has experienced generalized acute urticaria after an insect sting be prescribed self-injectable epinephrine^{4,5}; however, patients 16 years and younger who have experienced only cutaneous symptoms after an insect sting only have about a 10% chance of having another systemic reaction if resting and if a systemic reaction does occur it is unlikely to be worse than the initial isolated cutaneous reaction.^{3,6}

Patients with venom hypersensitivity and their family members have a significant burden of anxiety that affects quality of life.⁷ Although venom immunotherapy improves quality of life, the recommendation that anaphylaxis preparedness include an indefinite prescription for self-injectable epinephrine in venom-allergic children with strictly cutane-

ous symptoms does not improve quality of life.⁸ Whether to prescribe self-injectable epinephrine for a child with mild venom anaphylaxis is a decision that may involve trade-offs among preparedness, inconvenience, and anxiety.

Cost-effectiveness analyses are useful in the face of meaningful trade-offs by providing systematic comparisons of alternative strategies in an explicit and quantitative manner.⁹ Such an analysis provides a common metric to compare therapies used in different medical conditions, and benchmarks for cost-effective interventions have been described (therapies costing <\$100,000 per life-year gained are generally considered cost-effective).¹⁰ This analysis was performed to characterize the cost-effectiveness of annual prophylactic self-injectable epinephrine for children with mild venom anaphylaxis.

METHODS

Cohort simulations were used to evaluate the benefit of prophylactic self-injectable epinephrine for children with mild venom anaphylaxis. The base case in each scenario was represented by a 6-year-old child. Long-term survival was modeled using age-adjusted mortality from the 2002 US life tables¹¹ and the probability of a fatal insect sting reaction. A computer-based mathematical model (TreeAge Pro 2005 Suite; TreeAge Software, Inc, Williamstown, Massachusetts) was used to perform Markov modeling to reflect the natural history of children with mild venom anaphylaxis (Fig 1).

Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, and Center for the Evaluative Clinical Sciences, Hanover, New Hampshire.

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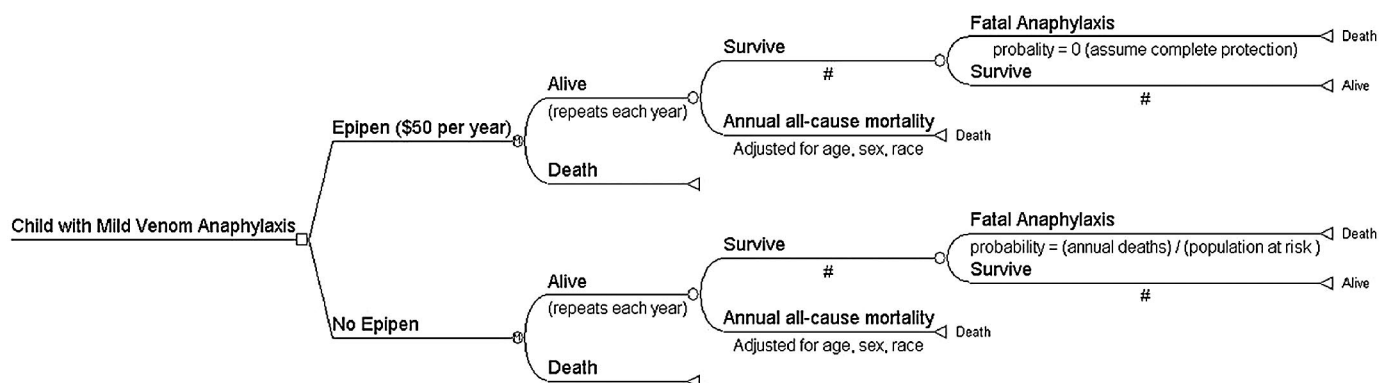


Figure 1. Natural history model. Hypothetical patients return to either Epipen or no Epipen each year and reexperience risks of all-cause mortality and anaphylaxis. Epipen indicates self-injectable epinephrine prescriptions.

Markov modeling is a decision-analytic model that incorporates a process derived from matrix algebra to describe transitions experienced by hypothetical cohorts of patients between defined health states over a linear time frame.⁹ It is useful in clinical circumstances characterized by recurring probabilistic risk. Markov modeling allows hypothetical patients to reexperience risks of anaphylaxis and all-cause mortality each year. With this technique, risk reduction can be evaluated in terms of costs of anaphylaxis preparedness. Because cohort simulations reflect probabilistic risks applied to populations, descriptive statistics of samples and sample size calculations are not appropriate or required. Sensitivity analyses were performed using a computerized iterative process to determine critical variable inputs associated with a change in cost-effectiveness (threshold cost-effectiveness values).

The model included these clinical and market assumptions.

1. Annual market costs of self-injectable epinephrine prescriptions (\$50) were obtained from an online commercial pharmacy.¹²

2. The mortality associated with venom anaphylaxis is uncertain. The stinging insect hypersensitivity practice parameter endorsed by the Joint Council of Allergy, Asthma, and Immunology estimates that at least 40 deaths result from venom anaphylaxis in the United States each year.⁴ The population at risk for fatal events was calculated using the prevalence of venom hypersensitivity (3%)^{4,13} and US census estimates (301,290,902 persons).¹⁴

Annual Fatality Rate

$$= \text{Annual Deaths/At-Risk Population (Adult and Pediatric)}$$

$$\text{Annual Fatality Rate} = 40/(0.03 \times 301,290,902)$$

$$= 4.4 \times 10^{-6}$$

The childhood fatality rate was estimated using mortality statistics provided by the Centers for Disease Control and Prevention (CDC). Venom associated mortality rates (*Inter-*

national Classification of Diseases, 10th Revision, code X23, contact with hornets, wasps, and bees) were stratified by age. Two hundred sixty deaths were reported to the CDC between January 1, 1999, and December 31, 2003. Three of these deaths were reported in children aged 1 to 19 years (average age-adjusted population, 35,937,705) during this period.¹⁵ The prevalence of venom hypersensitivity during childhood was used to calculate the population at risk (0.4%–0.8%).⁴ The annual venom fatality rate for children aged 1 to 19 years was 0.21 to 0.42 per 100,000 persons at risk:

Annual Fatality Rate

$$= \text{Annual Deaths/At-Risk Population (Pediatric)}$$

$$\text{Annual Fatality Rate} = 0.6/(0.004 \times 35,937,705)$$

$$= 0.6/(0.008 \times 35,937,705) = 2.1 \times 10^{-6} - 4.2 \times 10^{-6}$$

Using each of the previous methods, the fatality rate ranged from 0.21 to 0.44 per 100,000 persons. The highest fatality rate was used for base modeling assumptions.

3. Future costs and years were discounted at an equal rate of 3% per year to account for variance between future and present value of resources.¹⁶

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental cost of the self-injectable epinephrine strategy by its incremental effectiveness.

$$\text{Cost}_{\text{Epipen}} - \text{Cost}_{\text{No Epipen}} / \text{Effectiveness}_{\text{Epipen}} - \text{Effectiveness}_{\text{No Epipen}}$$

where Epipen indicates self-injectable epinephrine prescriptions.

RESULTS

The incremental cost of prophylactic self-injectable epinephrine was \$1,469 per patient. The incremental cumulative effectiveness of this strategy was 0.003 years per patient. The ICER was \$469,459 per year of life saved (Fig 2). The

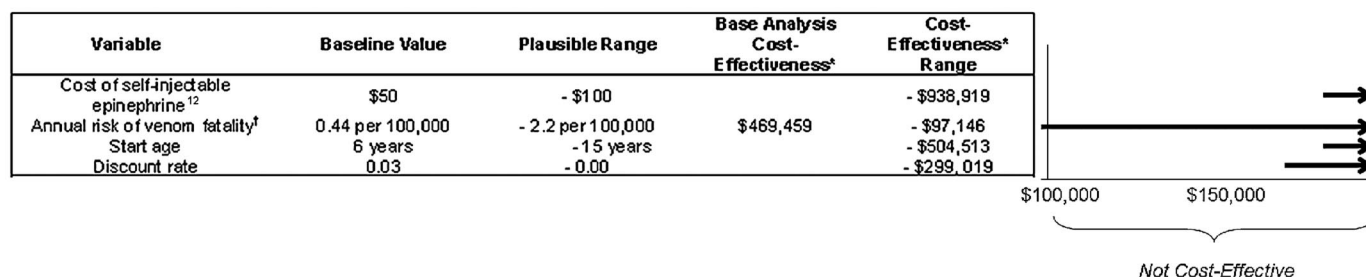


Figure 2. Cost-effectiveness of prophylactic self-injectable epinephrine prescriptions in children with mild venom anaphylaxis. The asterisk indicates cost per life-year saved; and dagger, fatality rates that were estimated using mortality statistics provided by the Centers for Disease Control and Prevention (CDC), the current stinging insect hypersensitivity practice parameter endorsed by the Joint Council of Allergy, Asthma, and Immunology, and current US census estimates.

strategy cost \$6,882,470 per death prevented when evaluated at a 40-year time horizon.

Cohorts at different ages were also evaluated in the sensitivity analyses. The therapy became more expensive as the cohort aged. For 15-year-old patients, the incremental cost was \$504,513 per life-year saved. At younger ages, the therapy remained expensive (ICER, \$459,645 for 3-year-old children).

Higher venom anaphylaxis fatality rates were modeled in the sensitivity analyses. When the annual fatality rate reached 2.2 per 100,000 allergic persons, the incremental effectiveness of this strategy increased to 0.015 years per patient. The ICER under these assumptions was \$97,146 per life-year saved. Self-injectable epinephrine was increasingly cost-effective at higher fatality rates. For example, the ICER was \$37,594 per life-year saved when the fatality rate reached 5.5 per 100,000 persons at risk.

Because prophylactic self-injectable epinephrine may not be prescribed indefinitely, we also modeled the cost of therapy over the first 5, 10, 20, 30, and 40 years of use. The cost of prophylactic self-injectable epinephrine exceeded \$100,000 per life-year saved at 5-, 10-, 20-, 30-, and 40-year time horizons because the cumulative risks of fatal anaphylaxis and costs of prophylactic epinephrine were reduced over shorter time horizons.

DISCUSSION

Guidelines recommend that children with mild venom anaphylaxis carry self-injectable epinephrine^{4,5}; however, such an approach may increase anxiety and undermine appropriate reassurance.⁸ This analysis was performed to evaluate the costs of anaphylaxis preparedness in children with mild venom anaphylaxis. The routine use of self-injectable epinephrine in every child with mild venom anaphylaxis was not a cost-effective intervention under base assumptions. If higher venom-associated mortality was assumed, the therapy was more cost-effective (the threshold was 2.2 deaths per 100,000 persons at risk).

Particular characteristics of individual patients may suggest an annual risk of fatal anaphylaxis that approaches or exceeds the threshold rate, and prophylactic self-injectable

epinephrine would be cost-effective in such situations. It is possible that some populations of children with mild venom anaphylaxis may have higher rates of resting reactions. In 1 retrospective cohort study,¹⁷ the rate of resting reactions reached 30% in children with mild anaphylaxis, with moderate and severe anaphylaxis occurring in 3.1% and 1.6% of patients, respectively. However, the risk of sudden, fatal, venom-associated anaphylaxis in children with mild venom anaphylaxis seems to be unusual.^{3,6} If self-injectable epinephrine is prescribed for children with mild venom anaphylaxis, consideration of repeat assessments of venom-specific IgE may be warranted to evaluate for the loss of venom sensitization. In some situations, the choice to prescribe self-injectable epinephrine will be a patient preference-sensitive decision and warranted practice variation may exist. In these instances, a process of shared decision making or the use of a patient decision aid^{18,19} may be appropriate.

It is tempting to speculate on the economic effect of other recommendations for prophylactic epinephrine for other patient populations at risk for anaphylaxis. Children with mild venom anaphylaxis represent a unique group of patients who tend to experience repeat episodes of venom anaphylaxis similar to their index reactions.^{3,6} In other circumstances for which prophylactic epinephrine is more commonly prescribed, episodes of anaphylaxis are more likely to worsen over time. For example, the tendency of children with food allergy to experience progressive anaphylaxis with repeat accidental food exposures is well documented. Vander Leek and colleagues²⁰ reported that among 26 children with peanut allergy whose index reaction was limited to cutaneous symptoms, 63% of subsequent reactions experienced involved more progressive symptoms. A more recent recommendation for prophylactic epinephrine has been made for patients receiving omalizumab; the incidence of anaphylaxis is estimated to be 1:1,000 patients.²¹ Once again, this population may be at greater risk for fatal anaphylaxis because this therapy is used in patients with moderate to severe persistent asthma, which is a risk factor for fatal anaphylaxis.^{5,22} In these and other circumstances, it is likely that the risk of fatal anaphylaxis exceeds the threshold reported herein and the

practice of prophylactic self-injectable epinephrine is likely to be cost-effective.

There are several limitations to the model. The model assumed single, indefinite, self-injectable epinephrine prescriptions were refilled annually. This assumption is consistent with the guideline recommendation, although practice variation likely exists in this regard. The actual costs of self-injectable epinephrine may be higher in many clinical circumstances, such as when multiple self-injectable epinephrine prescriptions are dispensed for individual patients. The model assumed universal protection from anaphylaxis-related mortality for patients with self-injectable epinephrine prescriptions. Although this is likely an overestimate, the direction of bias this assumption might introduce would tend to favorably affect the cost-effectiveness of prophylactic self-injectable epinephrine prescriptions. Even if universal protection does not occur, the cost-effectiveness of prophylactic epinephrine in this population would not be less than \$100,000 per life-year saved. Estimates of mortality were based on the prevalence of venom hypersensitivity,⁴ US census estimates,¹⁴ venom anaphylaxis fatality estimates,^{4,13} and venom-associated fatalities in children reported to the CDC.¹⁵ It is possible that many more venom-associated fatalities occur each year than those estimated in the Joint Council of Allergy, Asthma, and Immunology stinging insect practice parameter⁴ or reported to the CDC as a result of underreporting of venom anaphylaxis fatalities. However, even assuming a 4-fold increase in the estimated venom-associated anaphylaxis fatalities, the routine use of prophylactic self-injectable epinephrine would not be cost-effective for children with mild venom anaphylaxis. In fact, the approach used in this model may have overestimated the rate of fatal venom-associated reactions in children with mild anaphylaxis because it is derived from data that include individuals with more severe index reactions at greater risk for progressive anaphylaxis. The model did not incorporate economic disutility of anaphylaxis preparedness because, to my knowledge, the quality-of-life impairment associated with an epinephrine prescription has not been characterized in economic terms. Inclusion of health state utilities to reflect impairment in quality of life would likely decrease the cost-effectiveness of self-injectable epinephrine.⁸

The results of this study indicate that for many children with mild venom anaphylaxis, prophylactic self-injectable epinephrine to prevent fatalities may not be a cost-effective approach. However, the threshold annual venom anaphylaxis fatality rate at which this practice becomes cost-effective is low. Further research documenting the risk of sudden fatal anaphylaxis in this population and the role of shared decision making in anaphylaxis preparedness is needed.

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Requests for reprints should be addressed to:
Marcus S. Shaker, MD
Section of Allergy and Clinical Immunology
Dartmouth-Hitchcock Medical Center
1 Medical Center Dr
Lebanon, NH 03756
E-mail: marcus.shaker@dartmouth.edu