



An update on allergic emergencies

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Purpose of review

To provide an updated framework of management for allergic emergencies.

Recent findings

The most frequent causes of anaphylaxis include medications, foods, and stinging insects. Early and appropriate administration of epinephrine is critical to managing anaphylaxis. Although epinephrine is well tolerated and there is no absolute contraindication to using epinephrine in first-aid management of anaphylaxis, many patients at risk for anaphylaxis still fail to carry and use the medication prior to seeking emergency care. Outcomes of allergic emergencies can be improved by educational efforts that focus on adherence to emergency plans, as well as asthma controller treatments in patients with persistent asthma. Though venom immunotherapy is known to decrease the risk for stinging insect anaphylaxis, the role of emerging strategies for food allergen immunotherapy in reducing cases of anaphylaxis requires further study.

Summary

Fatalities resulting from anaphylaxis and asthma are rare. Patient education serves an important role in preparing for unexpected emergencies, instituting prompt and appropriate treatment, and incorporating effective strategies into the lives of children and families.

Keywords

anaphylaxis, asthma, epicutaneous immunotherapy, oral immunotherapy, venom immunotherapy

INTRODUCTION

Allergic disease is common and impacts quality of life through impairment, health beliefs, and perceptions [1,2,3^{*}]. Particular allergic diseases, such as asthma and/or allergy to a food, medication, or venom-containing insect sting predispose affected patients to the risk of severe and even life-threatening events [4,5^{*}]. Asthma affects 12–14% of children 6–14 years of age [6] whereas 4% of preschool children have challenge-proven food allergy [7^{**}] and 0.4–0.8% have an allergy to hymenoptera [8]. The annual childhood asthma-related fatality rate in the United States is estimated at 2.8 per million persons [9^{*}], whereas the rate of childhood food allergy fatality is 3.3 per million food-allergic persons [10]. Approximately 40 deaths from venom-containing stinging insects occur each year across all age groups [8]. Often underappreciated, drug allergy can also cause fatal anaphylaxis; however, older individuals with preexisting cardiovascular risk factors are at the greatest risk for this, with fatality rates increasing between 1999–2001 (general population risk of 0.27 per million persons) and 2008–2010 (0.51 per million) [11^{**},12].

ANAPHYLAXIS

Anaphylaxis is a medical emergency. Based on two nationwide surveys in the United States, the prevalence of anaphylaxis in the general population is at least 1.6% and may be as high as 5.2% [13]. In this study, medications accounted for 34% of anaphylaxis cases, with foods responsible for 31% and stinging insects for 20%. Although 42% of those surveyed sought treatment within 15 min of symptom onset, only 11% used self-injectable epinephrine, and only 10% called 911. In a review of nearly

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KEY POINTS

- Severe asthma exacerbations and anaphylaxis are common but fatalities rare.
- Patient education and partnership are critical for optimal management.
- Medications, foods, and stinging insects are common causes of anaphylaxis, and once anaphylaxis has occurred patients are at risk for repeated episodes.
- Allergen immunotherapy may protect against allergic emergencies in some settings, particularly for patients allergic to stinging insects.
- Administering epinephrine as early as possible in the case of a severe allergic reaction is potentially lifesaving.

2500 anaphylaxis fatalities from 1999 to 2010, common culprits were again medications, foods, and venom-containing stinging insects [12]. Another anaphylaxis registry of more than 4100 patients from 2006 to 2013 investigated how triggers for food-induced anaphylaxis differed between children and adults, finding that peanuts, cow's milk, and hen's eggs were common triggers in children, whereas wheat and shellfish were common triggers in adults [14]. Teenagers, persons with peanut/nut allergy, and persons with asthma are at greater risk for food allergy death [11[■],15,16]. Placing a patient upright during a resuscitation has also been noted to be a particular risk factor for allergy fatality because it can lead to the 'empty ventricle syndrome' when adequate cardiac preload is not maintained. Instead, patients should be placed in a recumbent position with the legs elevated during resuscitation [17].

Anaphylaxis is highly likely when one of three criteria is fulfilled: (1) sudden onset involvement of skin or mucosal tissue with respiratory symptoms and/or sudden reduced blood pressure; (2) at least two of the following after likely allergen exposure: sudden skin or mucosal tissue involvement, respiratory symptoms, reduced blood pressure, or gastrointestinal symptoms; or (3) reduced blood pressure after exposure to known allergen for that patient [18]. Anaphylaxis may result from immunoglobulin E (IgE) (such as in the case of medications, foods, and venoms mentioned above) or non-IgE immunological mechanisms (i.e., some cases of nonsteroidal anti-inflammatory drug-induced anaphylaxis), non-immunological mechanisms (such as direct mast cell mediator release in the case of exercise-induced anaphylaxis), and from idiopathic triggers. Age-related factors can increase the complexity of anaphylaxis. Infants cannot clearly describe symptoms

[19[■]], adolescents may engage in risk-taking behaviors, and elderly patients may have co-morbidities or use medications which impair compensatory mechanisms during anaphylaxis [18]. The atopic (or allergic) march of childhood which includes asthma, atopic dermatitis, and food allergy can be relevant in some cases of anaphylaxis because asthma itself is a risk factor for more severe anaphylaxis; however, atopic disease is not a risk factor for development of drug or venom allergy [20,21[■]].

Mast cell activation syndrome (MCAS) presents as episodic multisystem symptoms because of mast cell mediator release that may or may not meet the definition of anaphylaxis. Unlike systemic mastocytosis, MCAS is not a proliferative mast cell disorder, but represents a syndrome in which there are symptomatic features of mast cell release. Three criteria must be present for diagnosis of MCAS: (1) episodic multisystem symptoms consistent with mast cell activation, (2) response to medications targeting mast cell activation, and (3) increase in markers of mast cell activation during a symptomatic period when compared to baseline values [22[■]].

EPINEPHRINE

Epinephrine is the first-line medication of choice in anaphylaxis that should be injected intramuscularly in the mid-anterolateral thigh as soon as anaphylaxis is diagnosed or strongly suspected. Delayed epinephrine use is thought to be a risk factor for more severe anaphylaxis as well as anaphylaxis-related fatality [18,23[■],24]. In a study of canine anaphylaxis, if epinephrine was delayed and given during profound hypotension, its efficacy was lost, though no such data are available in humans [25]. During anaphylaxis, epinephrine targets α -1 and β -1 adrenergic receptors while stabilizing mast cells to decrease ongoing mediator release through β -2 adrenergic properties [18].

Unfortunately, despite advice to individuals at risk for anaphylaxis to carry an epinephrine auto-injector at all times, many patients who experience anaphylaxis do not use personal epinephrine before presenting for emergency evaluation [26,27[■]]. For example, in a study of children evaluating epinephrine use prior to emergency department arrival, only 36% of children received epinephrine prior to arrival. Interestingly, reactions occurring at home were less likely to be treated with epinephrine compared to reactions at school (odds ratio [OR], 0.29; 95% confidence interval [CI] 0.15–0.59). Surprisingly, the odds of receiving epinephrine prior to arrival was lower with two (OR, 0.5; 95% CI 0.3–0.85) or three organ system involvement (OR, 0.41; 95% CI 0.21–0.81) compared to one organ system

involvement [28²²]. One explanation for this association of more severe reactions with a lower rate of personal epinephrine use could be a tendency of patients to proceed directly to emergency care in lieu of appropriate epinephrine use. Though allergic reactions that do not promptly resolve with epinephrine use require immediate evaluation, the cost-effectiveness of routine observation of resolved reactions after immediate epinephrine use has been questioned. Together this evidence suggests that patients should be advised to first use epinephrine promptly in the treatment of community anaphylaxis and then activate emergency medical services (EMS) [29²³]. Although utility of preemptive epinephrine use before symptoms development has been questioned [30²⁴,31], EMS activation is not a substitute for using self-injectable epinephrine when symptoms develop. When EMS activation is used in this way it can paradoxically delay appropriate treatment.

Epinephrine may also be underused because of excessive cost [32] and recent challenges in availability [33]. The 400% price increase in epinephrine autoinjectors that has occurred since 2007 [32] remains somewhat enigmatic. Interestingly, despite these high costs, a recent survey of patient thresholds for emergency epinephrine sharing found that 79% of those surveyed reported annual household out-of-pocket epinephrine expenses less than \$200 [34²⁵]. Although this cost is still greater than the \$24 price tag recently shown to represent a value-based cost-effectiveness ceiling [35²⁶], it does demonstrate the range of out-of-pocket costs that families actually experience in the era of high-deductible health insurance plans. Whether or not novel models of epinephrine utilization in school settings may lead to improvements in availability remains an open question [36²⁷,37²⁸]. Additional clarification on expiration dates of epinephrine is also important, given the evidence that epinephrine solutions found in epinephrine autoinjectors that were no more than 24 months past the expiration date still contained at least 90% of the labeled dose [38]. Although patients should monitor expiration dates of autoinjectors and replace them when the date passes, they may use an outdated injector free of precipitate in an emergency, if the alternative is no epinephrine access [23²⁹]. Also of note, while it is recommended that epinephrine should be stored at room temperature (20–25°C with excursions to 15–30°C), recent reviews have found reassuring results on the effect of temperature on epinephrine. Prolonged heat exposure resulted in epinephrine degradation, but extreme cold did not (however, effects of extreme temperatures and freezing are not well studied). No studies evaluating real-world temperature fluctuations resulted in degradation [39].

A recent summary and simulation of adverse reaction to epinephrine rates confirmed both the safety of using this agent and the lack of any absolute contraindications to epinephrine use during anaphylaxis [40³⁰]. Adverse events from epinephrine use may result from dosing errors (more common with intravenous than intramuscular epinephrine), inadvertent lacerations, digital injection, and bone injuries. Reports to the Food and Drug Administration of adverse events from epinephrine autoinjectors have increased in recent years. Stress (Takotsubo) cardiomyopathy is a rare adverse event characterized by ST-segment elevation, elevated troponin levels, and apical hypokinesis on echocardiography that can present a management dilemma. Although the condition occurs primarily in elderly women, several cases linked to epinephrine in young adults have been reported. In contrast to Kounis syndrome, which results from coronary vasospasm associated with anaphylaxis, Takotsubo cardiomyopathy relates to epinephrine use, so clinicians must carefully weigh risks and benefits of additional epinephrine doses when managing patients with this condition [41³¹]. Although rare, Takotsubo cardiomyopathy is primarily associated with intravenous epinephrine administration. Injection site issues are the most common issue with autoinjectors. The most common site of accidental injection with the EpiPen/EpiPen Jr (Mylan Specialty, LP, Morgantown, WV) devices is the digit, whereas the leg/thigh are the most common sites for accidental injection with the Auvi-Q (Kaleo, Inc, Richmond, VA) devices [40³²]. However, laceration associated with EpiPen devices in particular (because the needle does not automatically retract) has been a recent concern, and because of such laceration risk [42], some epinephrine autoinjector labeling now recommends a 3-s hold instead of the prior 10-s hold and emphasizes the need to immobilize the child's extremity during injection [43].

ASTHMA

The 2018 Global Initiative for Asthma (GINA) Report continues to classify asthma as mild, moderate, or severe based on retrospective assessment of required treatment to control symptoms and exacerbations [44³³]. The recently introduced Pediatric Asthma Yardstick [45³⁴] provides a useful framework to consider asthma classification and treatment whereas still focusing on major domains of daily impairment and risk because of asthma. With normal lung function (forced expiratory volume 1 greater than 80%), asthma is considered mild intermittent if characterized by symptoms fewer than 2 days per week (and nocturnal symptoms less than

twice per month) [46]. With greater symptom frequency or impairment in lung function, persistent asthma can usually be managed with daily controller therapy, which may include everyday use of an inhaled corticosteroid, leukotriene modifier, combination of inhaled corticosteroid with a long-acting bronchodilator, or addition of a biologic such as omalizumab, mepolizumab, benralizumab, or dupilumab [45[■]].

Though 70% of patients with asthma on daily inhaled corticosteroids report using their medication all or most of the time when asymptomatic [47], rates are much lower when pharmacy claims are used to assess adherence. Notably, adherence can be improved with efforts to increase education. A recent study demonstrated significant improvements in both adherence (46.3% versus 67.9%, $P < 0.001$) and asthma control (15.7% versus 56.4%, $P < 0.001$) with asthma education by asthma educator certified pharmacists [48[■]]. Such efforts to promote adherence are important. A review of 108 pediatric asthma fatalities (ages 1–19 years) revealed that death occurred predominantly in 15–19 year olds, with nonadherence being most frequent among this age group [49]. Among all pediatric asthma fatalities, victims in all age groups (1–19 years) experienced a gradual deterioration during the month prior to the fatal attack, a more than 3-h length of final attack, and a delay in seeking medical attention during final attack. Additional risk factors included both poor perception of symptoms and broader socioeconomic disadvantages.

Acute severe asthma (formerly known as status asthmaticus) is defined as severe asthma unresponsive to repeated courses of β -agonists, and is a medical emergency that should be managed in coordination with a pediatric critical care team. The mainstays of treatment include: (1) aggressive bronchodilatory therapies, such as β -agonist therapies (both inhaled and intramuscular/intravenous), anticholinergics, and other smooth muscle/acetylcholine inhibitors (magnesium sulfate); (2) anti-inflammatory medications including early administration of corticosteroids; and (3) supportive measures, such as noninvasive positive pressure ventilation and/or helium–oxygen gas mixtures [50[■]]. In some circumstances, intubation and mechanical ventilation in asthma can be lifesaving, but should be done in conjunction with pediatric critical care because the transition from extreme negative pressure ventilation to extreme positive pressure ventilation can lead to severe pulmonary complications and catastrophic hemodynamic instability [51[■]]. Inhaled anesthetics can be utilized for their bronchodilatory properties after intubation [52], and extracorporeal membrane oxygenation

has been reported to be very successful as a rescue measure [53].

PREVENTION

Efforts to prevent allergic emergencies include strategies to avoid allergen triggers (e.g., foods, stinging insects, and medications) and in the case of asthma, prevent and treat underlying inflammation (through both the use of allergy testing to understand and avoid triggers, and the use of effective controller medication). As noted before, patients at risk for anaphylaxis should carry personal epinephrine, patients with asthma should keep albuterol on hand, and all patients should seek immediate medical care for severe symptoms. In addition, the role of primary allergy prevention has been explored through observational and interventional cohorts [54,55[■],56,57]. The best example of this has been demonstrated in primary prevention of food allergy through early food allergen introduction. Though older studies preliminarily suggested that early peanut consumption may be associated with a lower risk for peanut allergy [58], a recent 2015 randomized study of 640 infants (4–11 months of age) with severe eczema, egg allergy, or both demonstrated a lower prevalence of peanut allergy with early introduction (1.9% in the early consumption group versus 13.7% in the avoidance group, $P < 0.001$) [59]. Subsequently, the United States and Canadian guidelines adopted a tiered approach to early peanut introduction in high-risk infants, which involved screening infants with severe eczema and/or egg allergy prior to introduction [60[■]]. However, approaches in other countries vary and not all recommend such screening [61[■]]. Recent evidence suggests family preferences, fears, and trade-offs may impact these screening decisions [62[■]]. Food allergy screening for peanut is associated with greater societal costs and results in a higher overall prevalence of peanut allergy; however, screening may prevent some generally non life-threatening index reactions [61[■]]. Notably, screening may not be well supported by caregivers because of concern for unnecessary testing, over-medicalization of infant feeding, and undue complexity of food introduction [62[■]]. Although no national or international recommendations exist for screening infants with severe eczema for egg allergy, optimal health and economic benefits also seem to occur with early and gradual introduction without screening in this population [63[■]]. Similarly, screening siblings of children with peanut allergy was also not cost-effective unless the prevalence of sibling peanut allergy exceeded 11% in the United States and families perceived significant differences in quality

of life impairment that would result from index reactions at home compared to clinic [64^{***}].

Allergen immunotherapy is an important component of reducing the risk of severe allergic reactions to stinging insects [8]. In a review of 1033 children diagnosed with allergic reactions to insect stings between 1978 and 1985, Golden and colleagues [65] reported systemic reactions to Hymenoptera stings occurred in 3% of treated versus 17% of untreated patients ($P=0.007$). The effect was even more pronounced in patients with a history of moderate to severe index reactions (5% versus 32%, $P=0.007$). In this study, venom immunotherapy led to significant risk reductions even 10–20 years after treatment was stopped [65]. Similarly, use of allergen immunotherapy for food allergy has been gaining traction with oral and transcutaneous delivery systems. In a recent phase-3 trial, 67.2% study participants 4–17 years of age who received 24 weeks of therapy (300 mg of peanut protein maintenance dose) were able to ingest a dose of at least 600 mg of peanut protein (corresponding to 2–2.5 peanuts) without dose-limiting symptoms compared to 4% of placebo recipients. However, 95% of study participants experienced adverse events from the therapy itself, with 14% receiving epinephrine during active treatment [66^{***}]. In a phase-2 trial of epicutaneous immunotherapy, treatment success (defined as tolerance of 5044 mg peanut protein challenge or 10-fold increase in consumed dose) was achieved in up to 48% of study participants. Patch site reactions were common, but no reactions required epinephrine [67^{***}]. How these therapies will ultimately be leveraged in practice may depend on commercial costs, rates of sustained unresponsiveness, and patient preferences [68^{***}].

CONCLUSION

Although severe asthma exacerbations and anaphylaxis are encountered with some regularity in clinical practice, fatal outcomes are rare. Still, much can be done to facilitate improved partnerships with patients and families, given that even the rare fatalities are largely preventable. Although it is important to keep risk in perspective, ensuring that patients and families understand the benefits of taking simple steps to decrease the risk for severe exacerbations, anaphylaxis, and hospitalizations is a worthwhile investment. Children who experience severe asthma exacerbations or an episode of anaphylaxis benefit from having a pediatric allergist on their care team to identify allergen triggers, provide targeted education, review action plans and preventive therapeutic recommendations, and consider allergen immunotherapy when appropriate. Future

research investigating the trade-offs and preferences of patients and their families is needed to better understand how food allergen immunotherapy will be positioned in patient care delivery.

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Conflicts of interest

There are no conflicts of interest.

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