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Infant Anaphylaxis: A Diagnostic Challenge

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Abstract

Purpose of Review Infant anaphylaxis has been increasing in incidence; however, significant gaps in the literature remain. The aim of this article is to review the most recent literature pertaining to infant anaphylaxis and discuss recent findings related to epidemiology, diagnosis, management, and prevention.

Recent Findings There is no accurate report of the incidence and prevalence of anaphylaxis in infancy. Food is the most common trigger for infant anaphylaxis reported. The diagnosis of anaphylaxis in infants is often missed, and, even when the diagnosis is made, epinephrine continues to be under-utilized. An epinephrine autoinjector with a shorter needle and lower dose is now available for infants.

Summary Concise criteria specifically focusing on infant anaphylaxis is needed to streamline its diagnosis and management. Diagnosis is underrecognized in infants leading to improper treatment. When the diagnosis is made, epinephrine continues to be under-utilized and under-prescribed in infants.

Keywords Infant · Anaphylaxis · Epinephrine · Allergic reaction · Food-induced anaphylaxis

Introduction

Anaphylaxis is a life threatening, systemic allergic reaction occurring after ingestion of an inciting trigger [1]. Proper recognition and prompt treatment with epinephrine is pivotal to preventing progression of the reaction and reducing morbidity and mortality. The infant age group presents a diagnostic challenge due to vague symptoms upon presentation. Anaphylaxis, according to the National Institute of Allergy and Infectious Diseases (NIAID), is defined as fulfilling any of the 3 following criteria: (1) "acute onset of skin and/or mucosal involvement plus respiratory symptoms or decrease in blood pressure; (2) two or more of the following symptoms occurring rapidly after an exposure to a likely allergen for that particular patient: skin/mucosal involvement, respiratory involvement, decrease in blood pressure, persistent gastrointestinal involvement; (3) reduction in blood pressure after exposure to a known allergen occurring within minutes to hours" [1]. It is important to note that, specifically for infants, blood pressure measurements are based on age-specific measurements or more than 30% decrease in systolic blood pressure [1]. Infants are often unable to verbalize certain symptoms making it difficult to interpret their presentation. Additionally, infants are exposed to many new foods during a short period of time; therefore, with each new food, the possibility of an allergic reaction exists. There have been rare reports of anaphylaxis in infants exposed to allergens in breast milk [2, 3]. With newer guidelines recommending early introduction of allergenic foods, infants are likely to be exposed to an increased number of food allergens earlier than in the past [2, 4].

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Epidemiology

Anaphylaxis has been increasing in incidence in children, especially from birth to 2 years of age [5••]. In the pediatric age group, it has been estimated that the incidence of anaphylaxis is around 32 per 100,000 person-years with an estimated prevalence between 0.3 to 5.1% [6]. A recent systematic review aimed to determine global incidence and prevalence of anaphylaxis in children (< 18 years of age). Findings showed

incidence ranging from 1 to 761 per 100,000 person-years for anaphylaxis from all allergens and 1 to 77 per 100,000 person-years for food-induced anaphylaxis. The prevalence ranged from 0.04 to 1.8% for overall anaphylaxis and 0.3 to 1.2% for food-induced anaphylaxis [7]. An accurate estimate of prevalence has not been determined in the infant age group, and it is assumed that this diagnosis is frequently missed and/or misdiagnosed [5••]. Furthermore, this wide range reported can be attributed to inconsistencies in making the diagnosis and variability in defining anaphylaxis in different countries [7]. An observational study of a national US database from 2005 to 2014 showed increasing rates of emergency department visits for food-induced anaphylaxis, with infants and toddlers having the highest rate [8]. One retrospective analysis over 8 years found the incidence rate of anaphylaxis in infants (< 12 months old) increased by 19 times during the study period [9].

In one study of children presenting with anaphylaxis to an emergency department in Madrid, Spain, over a 2-year period, the frequency of anaphylaxis was highest in infants from 6 to 12 months of age [10]. In addition, there is a paucity of data coming from developing countries [7]. A better understanding of the true incidence of anaphylaxis in infants is needed.

Risk Factors

Risk factors for severe anaphylaxis in infants can include respiratory comorbidities such as asthma, laryngotracheobronchitis, and bronchiolitis [5••]. Additionally, anaphylaxis symptoms can be augmented with stress, such as that caused by fever or infection [5••]. History or diagnosis of eczema was not more common in infants, as compared to older children, in one retrospective study [11••]. Current literature and review of studies has not identified if certain conditions in infancy pose an increased risk for anaphylaxis, such as congenital heart disease, isolated eczema without history of food allergy, sensitization to allergens, or bronchiolitis, and/or reactive airway disease [12]. More studies are needed to understand whether other risk factors for anaphylaxis exist in infants.

Signs/Symptoms

Most common signs/symptoms in infants involve the skin, gastrointestinal tract, or respiratory tract [5••]. Although there is not often report of cardiovascular involvement in infant anaphylaxis, blood pressure measurements in infants are often not obtained and this could lead to missed recognition of anaphylaxis [5••]. In one retrospective review comprised of 47 infants, defined in this study as children less than 12 months of age, infants were found to have skin involvement, primarily hives, followed by vomiting as their most common signs/symptoms. Infants also were found to present with gastrointestinal symptoms more frequently compared to children older than 12 months of age (89%, $p = 0.006$) [11••]. One infant in that study did manifest hypotension and required 2 doses of epinephrine [11••]. A retrospective, multicenter study of Korean infants aged 0 to 2 years similarly found skin manifestations (98.6%) to be the most common system involved in anaphylaxis, but, in contrast to the prior study described, this was followed by respiratory (83.2%), and then gastrointestinal symptoms (29.8%). Signs involving the cardiovascular system were present in only 7.7% of cases; however, the blood pressure was measured in only 9.1% cases [13]. In another retrospective study, which included 161 infants in Turkey, skin manifestations were the most common symptom (90.9%) followed by respiratory (58.9%) and gastrointestinal symptoms (56%) [14•]. This study also noted, along with skin and GI manifestations, an increase in neurological signs/symptoms in the infant age group compared with older children [14•]. In another study comparing infants (defined as children ≤ 12 months of age), to preschool aged children, the primary symptoms in infants were skin manifestations, followed by gastrointestinal and then respiratory symptoms. It was also highlighted that hives, neurological signs/symptoms (such as change in behavior, irritability, etc.), and hypotension were more likely to occur in infants compared with the older children in the cohort. Twenty-one percent of infants in this study experienced hypotension as a sign, which is a higher rate than has previously been reported [15•]. While the overwhelming consensus is that infants are most likely to manifest skin, respiratory, and/or gastrointestinal symptoms, one must still be vigilant in assessing for neurological signs/symptoms and monitoring of vital signs, especially blood pressure with an appropriate sized cuff using age-specific criteria for interpretation (Fig. 1, Tables 1, 2).

Triggers

Food is the most common trigger for anaphylaxis in infancy [5••]. Specifically, cow's milk and egg are the most commonly reported culprits in several studies [9–, 10, 11••]. In a study of Turkish infants, cow's milk was the most common trigger, followed by tree nut, and then egg [14•]. In a study of children in Spain presenting to the emergency department with anaphylaxis, cow's milk was the most common trigger, followed by egg and then fruits and finned fish in the 0- to 12-month age cohort [10]. An analysis of the European Anaphylaxis Registry also found cow's milk and egg to be the most common triggers of anaphylaxis in the first 2 years of life [16]. A retrospective review over 10 years in northern Sweden found infants more likely to experience anaphylaxis to staple foods (defined as milk, egg, wheat, soy, and fish). The study also noted an increased incidence of food-induced anaphylaxis and an increase in allergic reactions to egg over the 10-year period (Fig. 2) [17].

Table 1 Common symptoms seen in infants with anaphylaxis and their differential diagnosis. Information adapted from Simons et. al. and Nunez et al. [5, 24]

Signs/symptoms	Differential diagnosis
Angioedema	Hereditary angioedema
	Infection (cellulitis)
	Nephrotic syndrome
Diarrhea	Gastroenteritis
Hives/rash	Contact dermatitis
	Erythema multiforme
	Mastocytosis
	Staphylococcal scalded skin
	Toxic shock syndrome
	Urticaria
	Viral exanthem
Hypotension	Septic shock
Neurologic	Accidental ingestion of drugs or alcohol
	Encephilitis
	Intracranial hemorrhage
	Meningitis
	Non-accidental trauma
	Seizure
Respiratory distress	Asthma
	Breath holding spell
	Bronchiolitis
	Croup
	Foreign body aspiration
	Laryngeal web
	Tracheo-/laryngomalacia
	Vascular ring
Vomiting	Food-induced protein enterocolitis syndrome (FPIES)
	Food poisoning
	Gastroenteritis
	Gastroesophageal reflux disease
Other	Apparent life-threatening event
	Munchausen syndrome by proxy
	Sudden infant death syndrome

Differences in feeding and cultural preferences of specific foods should also be considered. Rarely, infants may experience anaphylaxis due to antigens present in breast milk [2]. A recent literature review found 2 case reports of anaphylaxis to fish in exclusive breast-fed infants after maternal ingestion of fish. One case report described a 7-week-old who was exclusively breastfed with anaphylaxis to maternally consumed peanut [3]. This poses an additional challenge in deciphering the inciting trigger in an infant reaction, as maternal diet should be taken into consideration in breast-fed infants.

Although the majority of infant anaphylaxis is secondary to food triggers, other possibilities must still be considered when obtaining the history, such as exposure to medications/antibiotics, stinging insects, and vaccinations [12]. With increased interest in anaphylaxis occurring in the infant population, it is likely we will learn different triggers may exist.

Diagnosis

Making the diagnosis in infants can be complicated due to the factors listed above. Currently, there is no standardized laboratory evaluation recommended for the diagnosis of anaphylaxis. Diagnosis is based primarily on history, which in this case, must be obtained from a caregiver and physical exam [5••]. Differences and ambiguity exist in the diagnosis of anaphylaxis globally. Specifically, in the UK and Australia, having only skin and gastrointestinal involvement does not fulfill criteria for anaphylaxis, even with exposure to a known or likely allergen, and therefore epinephrine is not utilized [18]. These differences in anaphylaxis classification along with the sometimes subtle presentation make diagnosis in this age group particularly challenging and studying trends in the literature difficult, as there is not a standard definition being used universally.

Serum tryptase is sometimes measured in the emergency department setting; however, food-induced anaphylaxis does not usually lead to an increase in serum tryptase [1, 2]. Due to their immature and developing immune system, infants have a higher level of mast cells at baseline which may lead to an elevated serum tryptase, therefore using serum tryptase to determine anaphylaxis in this age group may not be as useful [2, 19]. Infants often cannot communicate their symptoms, which makes identification of this condition difficult. Additionally, several symptoms reported with anaphylaxis are commonly seen in infants who are otherwise well, such as vomiting, spit-ups, fussiness, or drooling [2, 12]. A thorough history, including identification of any triggers and timing/chronology of symptoms, is necessary to make this diagnosis, especially in this vulnerable population.

Management

Epinephrine

The mainstay of treatment for anaphylaxis is intramuscular epinephrine [1, 13]. Epinephrine is underutilized in general, but, especially in infants, due to a variety of factors and this under-utilization of epinephrine has long been reported. There may be parental fear about administering the epinephrine autoinjector, clinicians, and caregivers may not be able to fully gauge the severity of the reaction, or uncertainty about whether the medication is needed in that moment [4, 15]. The most common reason for not administering epinephrine was reported, in one study, as failure to properly identify the reaction [20]. One study of 512 infants from age 3 to 15 months, with known or likely allergy to milk or egg, reported 11.4% of

Table 2 Summary of recent original articles and findings of triggers, symptoms, and treatment in infants with anaphylaxis

Study	Summary	Number of Infants in study (age range)	Triggers in infants	Symptoms	Treatment/management	Autoinjector prescription
Samady, et al.	Retrospective review of children < 18 years over a 2-year period. Forty-seven cases of anaphylaxis in infants and 43 cases in toddlers	*N* = 47 (< 12 months)	Egg (38%), milk (17%), peanut (13%), unknown (13 %)	Skin involvement (94%), GI (89%), respiratory (17%), cardiac (2%)	Not available	Not available
Kahveci, et al.	Retrospective review of children ages 0–6 years with history of food-induced anaphylaxis in Turkey. There were 175 reactions in 160 infants in this study.	*N* = 160 (0–12 months)	Cow's milk (51.4%), tree nuts (16.6%), egg (15.4%), wheat (5.7%), lentil (5.1%), sesame (4.6%)	Skin involvement (90.9%), respiratory (58.9%), GI (56%), mucosal (45.1%), neurologic (14.9%)	Adrenaline administered in 40.6% on infants. H1 antihistamines (85.7%), corticosteroids (70.9%), B2 agonist inhalers (14.3%), IV fluids (6.9%), hospitalization (16%)	Autoinjectors prescribed 10 10.3% of infants.
Joen, et al.	Retrospective chart review of patients aged 0–2 years diagnosed with anaphylaxis between 2009 and 2013.	*N* = 363 (0–2 years)	Food (93.3%): cow's milk (43.8%), egg (21.9%), walnut (8.3%)wheat (7.7%), peanut (4.7%), other nuts (3%), fish (2.1%), soybean (1.8%), other (5.9%) drug (3%), food-dependent exercise induced (0.9%) insect bite (0.6%)	Cutaneous (98.6%), respiratory (83.2%), GI (30.2), neuromuscular (10.9), cardiovascular (7.7%)	Epinephrine (46.8%), antihistamine (82.3%), IV fluids (65.7%), corticosteroid (57.4%), bronchodilator (28%), oxygen (24.6%)	Epinephrine autoinjector prescription (25.1%)
Pouessel, et al.	Retrospective analysis of all cases of food related anaphylaxis in preschool children recorded in the Allergy Vigilance Network from 2002 to 2018. There were 59 infants in this study.	*N* = 59 (≤ 12 months)	Cow's milk (59%), egg (20%); raw egg (10%), wheat (6%), and peanut (3%)	Mucocutaneous (79%), GI (49%), respiratory (48%), hypotension (21%), neurologic (26%)	Adrenaline (25%), corticosteroid (41%), antihistamines (43%), bronchodilators (8%), hospital admission (65%)	Not available
Alvares-Perea, et al.	Observational, descriptive study of 133 cases of anaphylaxis presenting to a pediatric emergency room in Madrid, Spain	*N* = 20 (< 12 months)	Cow's milk (67%), egg (22%), fruits (6%), finned fish (6%)	Not available	Not available	Not available

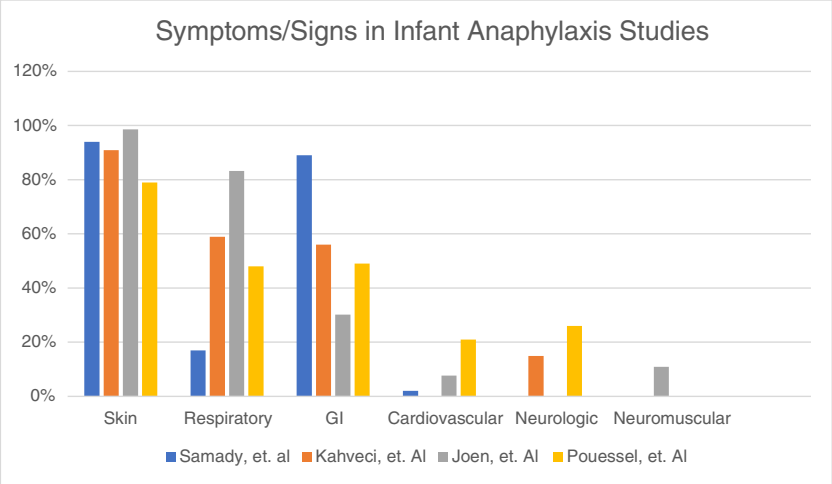

Fig. 1 Comparison of manifestations by organ system in infant anaphylaxis in recent reported studies

reactions classified as "severe," yet only about 30% of these severe reactions were treated with an epinephrine autoinjector [20]. Another study of infants, from birth to 2 years of age, found only 46.8% of cases of infantile anaphylaxis were treated with epinephrine and only 25.1% of cases received a prescription for an epinephrine autoinjector [13]. This finding was echoed in another study, where only 40.6% of infants with anaphylaxis received epinephrine (adrenaline) [14•]. A more recent study reported epinephrine (adrenaline) was used in only 25% of infants diagnosed with anaphylaxis, which is more concerning [15•]. One study by the authors found infants and toddlers were less likely to receive epinephrine in the acute setting compared to older children (odds ratio 0.32; 95% CI 0.13–0.75 (p = 0.009) (Pending publication)). (Melissa Cardenas-Morales, M.D., Balagangadhar R. Totapally, M.D., Vivian Hernandez-Trujillo, M.D.:Management of Anaphylaxis in a Tertiary-Care Pediatric Hospital Emergency Departments and Urgent Care Centers, unpublished)

The standard epinephrine autoinjectors on the market have, historically, only been available in two doses: 0.15 mg for children less than 30 kg and 0.30 mg for children and adults weighing 30 kg or more. With the lowest available dose being 0.15 mg, there may have been hesitancy to prescribe this dose for infants [21]. The 0.15 mg epinephrine autoinjector has been prescribed for infants in the past, as this was the lowest available dose, but this may provide up to double the recommended dose in infants less than 7.5 kg [21]. Infants may experience side effects with higher doses of epinephrine, i.e., jitteriness [22]. There has also been concern about the needle size and the possibility of striking bone with administration [22]. Previously, physicians had to either prescribe the dose of 0.15 mg epinephrine autoinjector or an ampule of 1 mg/ml of epinephrine with syringes in order to prescribe a lower dose of epinephrine. This practice relied on parents to draw up the weight base dose needed for their infant [23]. One study found many errors with parents drawing up the correct dose [23]. In

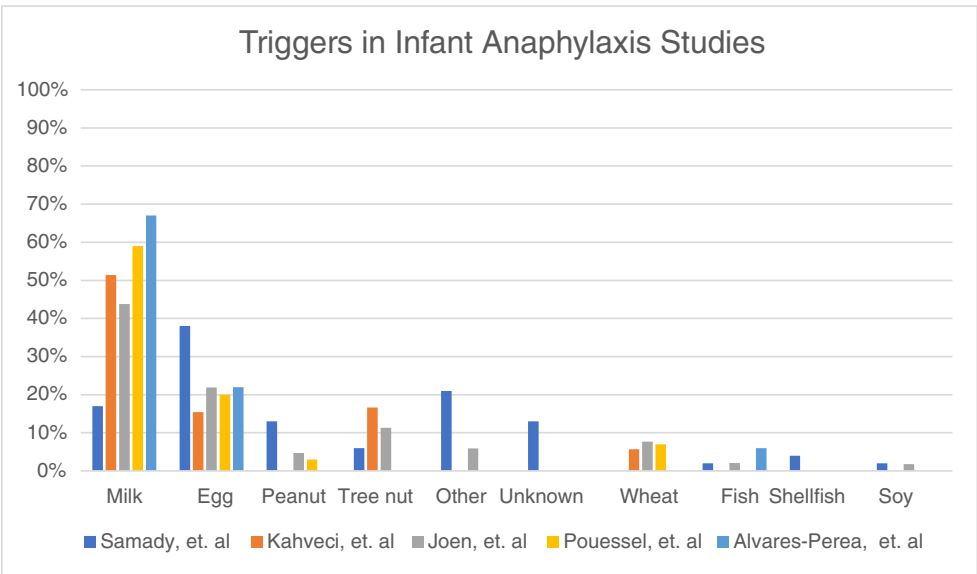

Fig. 2 Comparison of common triggers in infant anaphylaxis in recent reported studies

the hospital setting, infants should receive an appropriate dose of intramuscular epinephrine based on weight [22]. In 2017, the first epinephrine autoinjector with a smaller needle size was released at 0.1 mg dose for infants/children between 7.5 and 15 kg [12, 24, 25]. Studies investigating whether a difference in prescribing practice has occurred are needed.

Hospitalization for Anaphylaxis

In one retrospective cohort study of 7303 patients between the ages of 6 months to 18 years, patients less than 1 year of age were 1.8 times more likely to be admitted to the hospital when presenting with anaphylaxis ($p < 0.01$). This was thought to be due to perception of this age group as a vulnerable population by physicians and families [26]. A study of hospitalization trends for infants and toddlers presenting with anaphylaxis from 2006 to 2015 found a stable rate of hospitalizations during this study period (10 per 100,000 visits and 12 per 100,000 visits, respectively) [27]. Factors that increased the likelihood of hospitalization for anaphylaxis included male gender, private insurance, higher income, weekend day presentation, located in the northeast, presentation to a teaching hospital in an urban setting, and chronic pulmonary conditions, such as asthma [27]. Another study of pediatric emergency department visits and hospitalizations in Illinois found a 29.3% average annual increase in emergency department visits and hospitalizations for food-induced anaphylaxis from 2008 to 2012. Children in the 0 to 4-year age group had the most frequent ED visits annually [28]. With increasing numbers of young pediatric patients presenting to the ED, further studies will likely increase our understanding as to factors associated with increased hospitalization among the infant population.

Confirming the Cause of Anaphylaxis

A patient that has been treated for suspected anaphylaxis should have follow-up with an allergist to confirm the trigger of the episode. This is necessary to guide elimination of the allergen in the diet. A study by Alvarez-Perea et al. found that 39% of pediatric anaphylaxis cases had a discrepancy between the suspected cause of anaphylaxis in the pediatric emergency room and the confirmed trigger after allergy work up [10]. They also observed that, of the patients who were diagnosed with a particular food allergy in the ED, in 26% of the cases a different food was confirmed to be the trigger after allergy evaluation [10]. Although the 0 to 12-month age group had the highest degree of agreement between the suspected trigger in the ED and the confirmed trigger [10]. Although not stratified by age, one study of pediatric anaphylaxis cases over a 1-year period found only 30% ($n = 12$) of patients seen in the Emergency Department for anaphylaxis were referred to an allergist and only 4 of those patients were actually seen by the allergist [29]. Referral to the allergist will likely improve the proper diagnosis and identification of allergens in pediatric patients presenting with anaphylaxis.

Prevention

One randomized trial of early introduction of peanut to infants at risk for peanut allergy (defined as having severe eczema, egg allergy, or both) compared infants assigned to early consumption of peanut to infants assigned to peanut avoidance. The LEAP study found an 86.1% relative risk reduction in the prevalence of peanut allergy in the group of infants with initial negative skin test and 70.0% relative risk reduction in the prevalence of peanut allergy in the initially positive skin test [4]. In the LEAP-on study, participants from the primary study were instructed to avoid peanut for 12 months. This study found participants who had been introduced peanut during the first year of life, and consumed peanut until age 5, did not have an increase in peanut allergy after 12 months of peanut avoidance [30]. In one systematic review, early introduction in infancy of egg (between 4 and 6 months of age) and peanut (between 4 and 11 months of age) was associated with a decreased risk of developing egg and peanut allergy, respectively [31]. The EAT study looked at early introduction of six allergenic foods in exclusively breastfed infants, compared to infants who were exclusively breastfed until 6 months of age. When analyzing the data "per-protocol" rather than "intention to treat," it was found that the early introduction group had significantly lower prevalence of food allergy, allergy to peanut, and allergy to egg compared with the standard introduction group [32]. Further studies will be needed to assess adherence to these new recommendations regarding early introduction of allergenic foods and its effects on the incidence and prevalence of anaphylaxis in this age group.

Aside from preventing sensitization, education needs to be provided to parents regarding management of food allergies in food allergic children, with a focus on avoidance, label reading, and cross contamination, since, at this time, no treatment options exist for infants with food allergy. In one study, it was shown that the majority (87.4%) of infant anaphylaxis reactions were due to accidental exposure [6]. Another prospective study found that despite receiving education and instruction regarding avoidance of their infant's food allergy, 72% of the study participants subsequently had an allergic reaction [20]. This supports the need for improved education and frequent communication with parents and families of infants with food allergy.

Conclusions

Anaphylaxis is increasingly reported in the infant population, but there is no consensus on the diagnosis in this age group. There are inconsistencies among studies of infants with anaphylaxis as some studies classify infants as birth to 2 years of

age and others focus on children less than 12 months of age. The diagnosis is frequently missed due to the vague presentation of symptoms in this age group and the difficulty in infants communicating their symptoms. The phenotype most commonly described for infant anaphylaxis includes skin manifestations, especially hives, as the most common symptom. This is often followed by either gastrointestinal symptoms, especially vomiting, and/or respiratory symptoms. Cardiovascular symptoms, i.e., hypotension, may be missed in infants due to lack of monitoring. While difficult to assess, neurological symptoms, may also be missed in infants, as crying may be considered normal in this age group, but there may be a drastic change from baseline when anaphylaxis is the cause.

Infants are infrequently treated with the first line medication for the management of anaphylaxis, intramuscular epinephrine, and are less often prescribed an epinephrine autoinjector, as compared to older children. Studies are needed to assess prescription habits since the release of an epinephrine auto-injector with a lower dose, specifically, for infants, and whether prescription rates have increased in the infant age group.

Lastly, with anaphylaxis rates increasing in infancy, physicians should shift to focus on prevention and parental education. There should be emphasis on allergen avoidance, as well as indications for injectable epinephrine use, if an exposure occurs. Parents should be educated on signs and symptoms to look for that are different in infants, as compared to older children, so that the presentation may be recognized and appropriate treatment given.

Compliance with Ethical Standards

Conflicts of Interest Dr. Melissa Cardenas-Morales declares no conflict of interest. Dr. Vivian Hernandez-Trujillo has been on the advisory board for Kaleo, US World Meds, DBV and she is a spokesperson for Kaleo.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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