

Comparison of the Incidence, Etiology, and Management of Anaphylaxis Over Time

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Background: Failure to promptly recognize and treat anaphylaxis can result in death. Understanding the incidence, etiology, and management is imperative. A previous pediatric study identified latex as the most common anaphylaxis allergen. We aim to describe the incidence, etiology, and management of anaphylaxis prelatex and postlatex-precaution implementation.

Methods: Retrospective review of inpatient and emergency department (ED) records of pediatric anaphylaxis patients seen at 1 institution between 1986 and 1990 or 2002 and 2006 was performed. Patients with 2 systemic symptoms (gastrointestinal, respiratory, hypotension/syncope, oropharyngeal, altered mental status) or 1 systemic symptom plus 1 cutaneous symptom (urticaria, edema, or flushing) were included.

Results: Fifty-three episodes were included from 1986 to 1990. A total of 117 episodes were included from 2002 to 2006. Approximately 80% of cases presented to the ED. From 1986 to 1990, we noted 30.5 cases per 100,000 ED visits versus 38 cases per 100,000 ED visits from 2002 to 2006. Food allergens were most common in both groups (43%). Latex accounted for only 1.9% of cases in 1986 to 1990 versus 1.7% postlatex precautions. Prehospital epinephrine use was poor. Patients in 2002 to 2006 were more likely to receive steroids, H2-blockers, epinephrine auto-injectors, and allergist referrals but less likely to receive epinephrine.

Conclusions: The etiology of pediatric anaphylaxis has not significantly changed over time but seems to differ across regions because latex was not a significant allergen at this institution in either period. The incidence of anaphylaxis has increased slightly. Anaphylaxis remains underdiagnosed and undertreated. Improved education of patients/caregivers and health care providers is needed.

Key Words: anaphylaxis, allergy, food allergy, latex

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Anaphylaxis is a severe, potentially fatal, systemic allergic reaction characterized by rapid onset. Anaphylaxis is a common problem affecting up to 2% of the population with the largest incidence in children and adolescents.¹ In 2006 the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) published a set of clinical criteria for the diagnosis of anaphylaxis. Appropriate management was also described and includes the use of intramuscular epinephrine, β -adrenergic agonists, intravenous fluid resuscitation, H1 and H2 antihistamines, corticosteroids, placing the patient in a sitting position, appropriate observation, and potentially vasopressors or glucagon.² Despite the fact that immediate recognition and treatment of anaphylaxis is crucial to survival, poor adherence to these diagnosis and treatment recommendations

in academic pediatric emergency departments (EDs) has been reported.³ Other studies have shown that simple factors including patient age (adolescence) and lack of prompt epinephrine administration are associated with a greater incidence of biphasic reactions,⁴ morbidity, and mortality.⁵ Understanding anaphylaxis epidemiology, treatment and outcomes is a critical step toward improving the morbidity and mortality associated with this disease.

A 1997 retrospective study identified the causative agents of anaphylaxis in 50 pediatric patients presenting to a tertiary care children's hospital in the early nineties. Latex was identified as the most common agent responsible for anaphylaxis (27%), followed by food (25%), drugs (16%), and venoms (15%).⁶ Several studies have since suggested that food allergens are becoming increasingly more common etiology of anaphylaxis.^{7–9} Other studies suggest that the incidence of anaphylaxis itself is on the rise, particularly in children, and the etiology and incidence of anaphylaxis varies by geographical region.^{10–15} For example, although rarely seen in North America, severe sesame allergy is much more common in Israel than peanut allergy.¹⁴ This suggests that genetic factors, culture, dietary habits, and environmental exposures may play a role in the development of type I hypersensitivity reactions. With such changes occurring in a given community over time, one might expect a changing incidence and etiology of anaphylaxis.

In 1992, a standardized latex avoidance protocol was introduced at a pediatric tertiary care hospital in Chicago, IL, and resulted in a 3-fold decrease in risk of latex allergic reaction.¹⁶ There has also been a significant decrease in latex-specific immunoglobulin E in patients born after initiation of primary latex prophylaxis, suggesting a decrease in latex sensitization, despite multiple surgical procedures.¹⁷ There are few data, however, describing how the etiology of anaphylaxis has changed since latex avoidance measures were initiated. The aims of this study were to examine the changes in etiology of anaphylaxis prelatex and postlatex avoidance protocol, to examine hospital staff recognition of anaphylaxis, and to evaluate consistency of treatment and adherence to NIAID/FAAN treatment recommendations.

METHODS

This was a retrospective chart review of medical records of children 0 to 17.9 years of age seen in ED, surgical, or inpatient unit at a tertiary care children's hospital in Chicago, IL, with a diagnosis suggestive of anaphylaxis. Two periods were studied 1986 to 1990 (prelatex precautions) and 2002 to 2006 (postlatex precautions). Pertinent medical records were identified by *International Classifications of Diseases, Ninth Revision (ICD-9)* codes for anaphylaxis, allergic shock, anaphylactic reaction, drug reaction, anaphylactoid reaction, and allergic reaction not otherwise specified (*ICD-9* codes 995.0, 995.2–995.3, 999.4, 995.6–995.69, 996.4, V15.08). Medical record types included paper charts, microfiche records, and electronic health records.

Case Definition and Selection

All obtainable records were reviewed and pertinent cases were identified using the 2006 NIAID/FAAN clinical criteria for the diagnosis of anaphylaxis, which is as follows.

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TABLE 1. Study Demographics

	1986–1990	2002–2006
Male	51%	59%
Median age	6.9 y (6 mo to 16.2 y)	7.2 y (4 mo to 17.7 y)
ED	81%	80%
Inpatient	19%	20%

Anaphylaxis is highly likely when any one of the following 3 criteria is met:

1. Acute onset of an illness with the involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, pruritis, flushing, swollen lips, tongue, or uvula) AND at least one of the following: respiratory compromise, reduced blood pressure (BP), or associated symptoms (syncope, hypotonia, or incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen. Involvement of the skin mucosal tissue, respiratory compromise, reduced BP or associated symptoms (syncope, hypotonia, or incontinence), or persistent gastrointestinal symptoms.
3. Reduced BP after exposure to known allergen (for infants and children a low age-specific systolic BP or greater than 30% decrease in systolic BP); for adults, systolic BP less than 90 mm Hg or greater than 30% decrease from the patient's baseline.

Subjects were excluded if they did not meet the multisystem criteria for the diagnosis of anaphylaxis or if symptoms were not acute in onset.

Data Collection

Extracted data included demographic information, risk factors for anaphylaxis, documented history of allergy, documentation of exposure to a particular allergen, place of exposure, home epinephrine autoinjector availability and use, and each subject's clinical presentation. Treatment course, documentation of anaphylaxis education, home epinephrine autoinjector prescription, and allergist referral on discharge were also reviewed.

Statistical Analysis

Statistical analysis was performed via SPSS version 18.0 (SPSS, Inc, Chicago, IL) using frequencies, χ^2 statistics, and Fisher exact test where appropriate. Billing data were used to determine the total number of ED visits per period, and the incidence of anaphylaxis was calculated for each period per 100,000 ED visits.

RESULTS

A total of 1512 potential subjects were identified; 568 records from the 1986 to 1990 period were identified, 539 were reviewed, and 53 cases were included. Of the records from the 2002 to 2006 period, 944 were identified, 938 were reviewed, and 117 cases were included. Thirty-five records could not be located. Cases were excluded if they did not meet multisystem anaphylaxis criteria, if they were not acute in onset, or if the health record could not be located for review.

Demographics

The study populations did not differ significantly between the 2 study periods (Table 1). The mean age was approximately 7 years in each period. There was a male predominance (59%) in the later period. Approximately 20% of the documented cases of anaphylaxis occurred in the inpatient or surgical setting, whereas 80% presented to the ED.

Allergen Type

The etiology or suspected allergens responsible for anaphylaxis (Table 2) did not differ significantly between the 2 periods. Interestingly, latex was not identified as a significant allergen in either the prelatex or postlatex precaution period. The percentage of anaphylaxis cases related to food allergens also did not differ significantly between periods. Peanuts, tree nuts, milk, eggs, wheat, fish, and shellfish were the most commonly identified food allergens. Although there were slightly more peanut reactions in the earlier period and more tree nut reactions in the later period, this did not reach statistical significance (Fig. 1). Although the number of cases of anaphylaxis attributed to drug allergens was small in both periods, there is a suggested trend of change in drug allergens with antibiotics being most common in the earlier period and ibuprofen and infliximab being most common in the later period (Table 3).

Clinical Features

Facial edema was the most common presenting symptoms, present in 79% of patients, followed by urticaria in 70%, respiratory complaints in 66%, and gastrointestinal complaints in 34%. Flushing occurred in at least 14%, and syncope or symptoms of presyncope were described in 9%. Hypotension and mental status changes were less common and more difficult to assess given poor documentation of BP and neurologic examination.

Place of Exposure

Place of exposure was documented in 70% of cases; home was the most common place of exposure. Of those patients who came into contact with the inciting allergen outside the hospital, 76% reported exposure at their home. Only 5% had known exposure at school or day care.

Home Epinephrine Auto-injector Availability and Use

We then evaluated ED management of patients presenting with symptoms of anaphylaxis. The records were reviewed for comments on home epinephrine autoinjector availability and use before arrival in the ED. Although this information was documented in less than 48% of cases, significantly more families in the later period reported that they had an epinephrine autoinjector available at their home (Fig. 2). Presuming that only those children with a history of anaphylaxis or known allergy would have an epinephrine autoinjector available for self-administration at home and presuming wider availability of the home autoinjector in the 2002 to 2006 period, we performed the same calculation on the subset of subjects in the 2002 to 2006 period who had

TABLE 2. Etiology of Anaphylaxis

Suspected Allergen	1986–1990	2002–2006
Food	43.4	42.7
Latex	1.9	1.7
Insects	5.7	2.6
Drugs	30.2	16.2
Exercise	0	0.9
Allergen-specific immunotherapy	1.9	0.9
Other	3.8	6.5
Unknown	13.2	29.1

Anaphylaxis allergens based on patient or caregiver report of exposures before the onset of anaphylaxis symptoms.

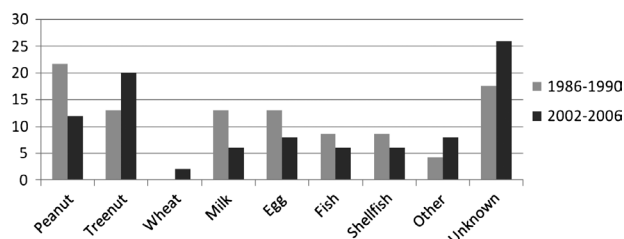


FIGURE 1. Etiology of food-related anaphylaxis. Food allergens causing anaphylaxis based on patient or caregiver report of exposure and/or known allergens. The y axis represents percent of total allergens. "Other" includes less common, but identified allergens such as "beans" or combination foods such as "macaroni and cheese." The "unknown" category includes those subjects whose allergen was either not identified by the caregiver or not documented by the medical provider.

a documented history of other known allergens. Still, only 16 of 23 subjects were questioned about epinephrine autoinjector at home, and 14 subjects reported that they had one. Nine of these subjects (64%) had self-administered epinephrine before arrival in the ED. Owing to the retrospective nature of this study, we were not able to determine the reason for limited use.

Diagnosis and Overall Incidence of Anaphylaxis

Emergency department visits were analyzed independent of the inpatient visits to determine the incidence of anaphylaxis for each period. An increase in the incidence of anaphylaxis was noted with 30.5 cases per 100,000 ED visits from 1986 to 1990 and 38 cases per 100,000 ED visits from 2002 to 2006. Although we found a total of 170 cases that met NIAID/FAAN criteria for a diagnosis of anaphylaxis, only 31.2% of these cases received a diagnosis of "anaphylaxis" from the treating physician. The most common diagnosis was "allergic reaction."

Emergency Department Management

Emergency department management of anaphylaxis in the prelatex precaution period was 1.9 times more likely (95% confidence interval [CI], 1.4–2.5) to include epinephrine. However, patients seen during the more recent period were 4 times more likely to receive steroids (95% CI, 2.0–7.9) and 10 times more likely to receive H₂ blockers (95% CI, 1.4–7.2) (Fig. 3). There was not a statistically significant difference in the rate of admission between the 2 periods. Of the subjects who were discharged home from the ED, greater than 87% were observed for less than or equal to 4 hours despite the fact that the NIAID/FAAN

TABLE 3. Drug-Related Anaphylaxis

Drug	1986–1990 (n = 14)	2002–2006 (n = 20)
Penicillin	4 (25.2%)	0
Cephalosporin	2 (12.6%)	2 (10.6%)
Other antibiotic	3 (18.9%)	3 (15.9%)
Ibuprofen	0	6 (31.6%)
Infliximab	0	3 (15.9%)
Other	5 (44.1%)	6 (30.8%)

Drug allergens causing anaphylaxis by patient or caregiver report or hospital chart documentation of exposure before anaphylaxis event and/or presumed by physician to be the etiology of the anaphylactic response.

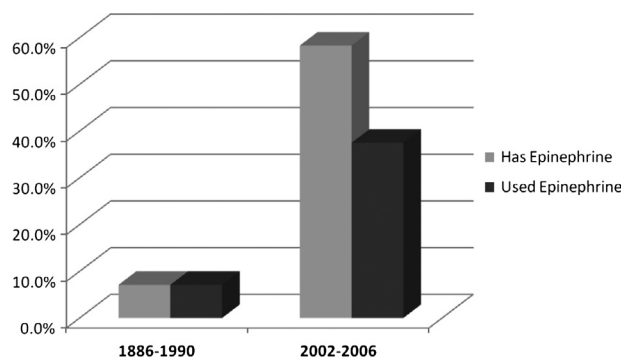


FIGURE 2. Prehospital (caregiver) epinephrine autoinjector use in ED patients with anaphylaxis. Data on home epinephrine autoinjector availability and/or use by caregivers was documented in fewer than 48% of records when limited to subjects who had a known history of allergic reaction. The difference in home epinephrine autoinjector availability between the 2 periods was statistically significant ($P = 0.005$).

guidelines state that "a reasonable length of time to consider observing the post-anaphylactic patient is 4 to 6 hours in most patients, with prolonged observation times or hospital admission for patients with severe or refractory symptoms."³ Physical positioning and initial BP were not consistently recorded, making analysis of these variables difficult.

Discharge Instructions and Outpatient Management

Lastly, we reviewed the discharge instructions, management recommendations, and follow-up instructions on all patients discharged from the ED. We limited this analysis to children with no known history of anaphylaxis or previous allergens, assuming that these patients were most in need of resources and outpatient medications, whereas children with a known allergy may already have a home epinephrine autoinjector and therefore not require a new prescription. Children who were seen during the more recent period were 3.6 times more likely to receive a prescription for an epinephrine autoinjector (95% CI, 1.5–9.7) and 2 times more likely to be referred to an allergist (95% CI, 1.4–4.0) compared with those seen between 1986 and 1990 (Fig. 4), although

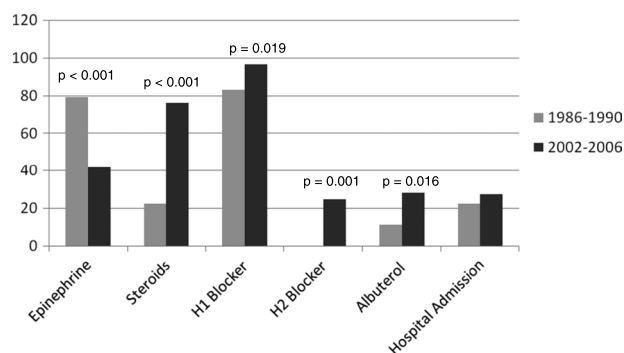


FIGURE 3. Clinical management of anaphylaxis in the ED. Six different areas of treatment were evaluated for subjects presenting to the ED with anaphylaxis during each period. The y axis represents percentage of total subjects. P values indicate statistically significant results.

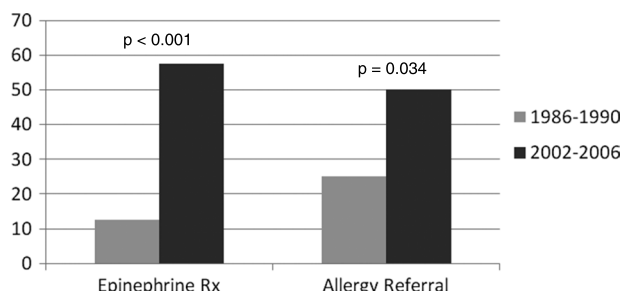


FIGURE 4. Discharge and outpatient management of ED patients with anaphylaxis. Data collected from ED charts and discharge paperwork. The y axis represents percentage of total population with no known history of allergies or previous episodes of anaphylaxis. P values are listed for statistically significant results.

both were documented in fewer than 58% of the children with anaphylaxis.

Limitations

This study is limited by its retrospective nature. Documentation was often limited, and we were not able to locate all of the necessary records. Only single-institution data were available, and data were subject to reviewer interpretation. This is not a study of adherence to clinical guidelines but rather a description of etiology and treatment of reactions over time.

DISCUSSION

This study provides a comprehensive review of incidence, etiology, and management of anaphylaxis as it has changed pre-universal latex and post-universal latex precautions intervention at a single pediatric tertiary care center. Historically, the study of anaphylaxis has been difficult owing to a lack of an agreed upon set of criteria for diagnosis of anaphylaxis or treatment recommendations until recently. This has led to a variance among physicians in the treatment of the disease based on perceived seriousness of illness or threat. We have reviewed a broad range of ICD-9 codes to capture all cases that meet the current diagnostic criteria for anaphylaxis, regardless of the discharge diagnosis.

Our data again suggest physician underrecognition and undertreatment of anaphylaxis. Only 31.2% of the cases that met the NIAID/FAAN criteria for the diagnosis of anaphylaxis were given a discharge diagnosis that included “anaphylaxis.” Instead, the most common diagnosis was simply allergic reaction. We are limited by the fact that our determination of anaphylaxis is based on recorded health record data and retrospective judgments; however, our data also show a link between underrecognition of anaphylaxis and undertreatment of the disease. For example, patients who received a diagnosis of “anaphylaxis” were overall 1.9 times (95% CI, 1.4–2.4) more likely to receive epinephrine than those who received a diagnosis of allergic reaction. This finding was even more profound in the later period when patients diagnosed with anaphylaxis were 3 times (95% CI, 1.8–4.8) more likely to receive epinephrine.

Although epinephrine remains the mainstay of treatment of anaphylaxis,^{18–20} our study shows an alarming trend toward the increased administration of antihistamines and steroids, with a concurrent decrease in epinephrine administration. More frequent use of epinephrine in the earlier period may be explained by standard of care at the time. With fewer alternative therapies available, subcutaneous epinephrine was a first-line therapy for more diagnoses. For example, a patient presenting with an asthma exacerbation or urticaria without any other symptoms of anaphylaxis

was much more likely to receive subcutaneous epinephrine than such a patient would today. This suggests that antihistamines and steroids are being used instead of epinephrine, despite lack of evidence for the use of these medications as first-line treatment in anaphylaxis. It is also alarming that home epinephrine auto-injectors are being prescribed in fewer than 58% of the patients that should have this lifesaving medication with them and available at all times.

This study again suggests an increase in the overall incidence of anaphylaxis presenting to the ED but does not speak of the overall prevalence of anaphylactic allergies. Interestingly, latex precautions do not seem to have had a profound effect on the incidence of latex-related anaphylaxis at our particular institution, although the incidence of anaphylactic reactions to latex was already low before any intervention. With such small numbers of latex-related anaphylaxis, it is difficult to make conclusions about the effectiveness of latex precautions. Overall, the allergens responsible for anaphylaxis remain unchanged, but our data on the etiology of anaphylaxis differ from other studies, supporting the theory of regional variation. Therefore, prevention strategies may be most effective if region-specific measures are considered.

CONCLUSIONS

In conclusion, there is a need for improved education of physicians and trainees in recognition and appropriate treatment of anaphylaxis. The electronic health record may also serve as a convenient tool for improving adherence to anaphylaxis treatment guidelines. A standardized allergic reaction order set that approaches treatment recommendations via an algorithmic approach could prompt physicians to order medications based on the symptoms that are present. Further research into caregiver reasons for deferring epinephrine autoinjector use is also needed. If discomfort or fear associated with the injection is a common problem, then more comprehensive patient and family education on epinephrine autoinjector self-administration is indicated. If families report that the autoinjector was not available at the time of the exposure (ie, the family was not at home and had not taken it with them), then further research into packaging, ease of transport, medication stability, and/or reminder mechanisms and effectiveness of these measures may be indicated. Lastly, although careful education of day care providers and school staff remains important, programs that serve to better educate and support parents and families of children with anaphylaxis or improved food labeling may be more effective in reducing recurrences because most of the allergen exposures that we have described took place in the home environment.

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