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Inpatient interventions are infrequent during pediatric hospitalizations for food-induced anaphylaxis

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To the Editor

Food allergy is increasingly prevalent and the most common cause of anaphylaxis in children (1). Although there have been significant increases in hospitalizations due to food-induced anaphylaxis (FIA) (2), there are sparse data on what transpires during a typical FIA hospitalization and evidence-based recommendations on which patients require hospitalization are lacking. Therefore, we sought to describe the clinical course of children hospitalized with FIA and to determine whether any factors could help predict those that will require significant inpatient interventions.

This retrospective cohort study was conducted at Hasbro Children's Hospital, an 87-bed pediatric tertiary referral center in Providence, Rhode Island, with ~48,000 Emergency Department (ED) visits/year. We reviewed the medical records from all patients <18 years who were hospitalized (observation or full admission status) with FIA between 1/1/04 and 12/31/12. Cases were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9) diagnosis codes (3). A standardized data abstraction form was used and all cases were reviewed by a board-certified allergist/immunologist. The local institutional review board approved the study.

A food-induced allergic reaction was defined as acute allergic symptoms (<72 hours) whose onset was within 2 hours of the food trigger. FIA was defined as a food-induced allergic reaction that met criteria for anaphylaxis as established by the National Institute of Allergy

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and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) guidelines (4) or that resulted in hospitalization. A significant inpatient intervention was defined as receipt of: 1) epinephrine (intramuscular, subcutaneous or intravenous), 2) a significant respiratory intervention (i.e. inhaled albuterol, inhaled racemic epinephrine, oxygen delivery or intubation), or 3) a significant cardiovascular intervention (i.e. use of vaso-pressors or IV fluid resuscitation).

Analyses were performed using Stata 14.0 (Stata Corp, College Station, TX). Unadjusted analyses were done using chi-square, Fisher's exact, and Kruskal Wallis tests, as appropriate. Multivariable logistic regression was used to evaluate independent predictors of receiving significant inpatient interventions. Factors were evaluated for inclusion if associated with the outcome in unadjusted analyses ($P<0.20$) or potentially clinically significant. All P values are two-tailed, with $P<0.05$ considered statistically significant.

Over the nine years, there were 100 FIA hospitalizations. The median patient age was 3.8 years (IQR 1.4-10.2) and 67% were male. The medical histories and clinical presentations are summarized in Table e1. Only 7% of patients were hospitalized for >1 day and only 7% of patients spent any time in an intensive care unit (Table 1). A similarly small percentage of patients (8%) had signs/symptoms documented during their hospitalization that met NIAID/FAAN anaphylaxis criteria. Accordingly, few patients (16%) received a significant inpatient intervention. Specifically, these patients received epinephrine (3% IM and 2% IV), inhaled albuterol (12%), supplemental oxygen (4%), inhaled racemic epinephrine (1%), and IV fluid boluses (2%). No patients required either ventilator support or vasopressors.

Several factors were associated with increased frequency of inpatient interventions on bivariate analysis (Table 2). Patients who received inpatient interventions were older and less likely to be white than those who did not. They were more likely to own an epinephrine auto-injector, to have a tree nut or shellfish trigger and to have asthma. They did not differ with respect to other aspects of the medical history, details of the current reaction, or pre-ED and ED management. After adjusting for age, sex, and race, patients with asthma remained at significantly increased risk (OR, 6.86; 95% CI, 1.64-28.75; $P=0.008$).

In the current study, we report that FIA hospitalizations are typically brief and significant inpatient interventions are infrequent – occurring in only 16% of those hospitalized. In our study, almost all (92%) of the patients' symptoms had resolved while in the ED suggesting that most were admitted due to a concern for a biphasic phase rather than severe/protracted symptoms. Current estimates on the rate of biphasic reactions vary widely and there remains a lack of consistency between studies regarding reliable clinical predictors (5). In this study, neither presenting signs/symptoms nor treatments received before hospitalization (pre-ED or ED) were associated with receiving inpatient interventions. Instead, we report that on multivariable analysis, patients with comorbid asthma had an increased risk of inpatient intervention. This coincides with previous observations that asthma was a common thread in fatal FIA (6). A better understanding of the frequency and risk factors for biphasic reactions would facilitate informed decisions about hospitalizing FIA patients whose symptoms have already responded to ED treatments.

Decisions about hospitalization for FIA also require consideration of illness severity and risk of fatality. In our study, severe presentations were uncommon. Only 7% of children received care in an intensive care unit. No patients received the most intensive types of medical interventions (i.e. intubation or vasopressors) and there were no deaths. This mirrors recent epidemiologic studies that have reported that although hospitalizations for anaphylaxis have been increasing, the incidence of fatal anaphylaxis has not increased in parallel (7).

Study limitations include the retrospective design. Specifically, issues with documentation make it difficult to assess the exact nature and timeline of inpatient symptoms. Due to this shortcoming, we chose to focus on inpatient interventions as there is typically less ambiguity in the documentation of medical therapies; however, we acknowledge that this may be subject to provider variation. Second, we acknowledge that there is subjectivity in our definition of “significant inpatient intervention” and that we have chosen a more liberal definition (including any inhaled albuterol) to capture more interventions. Although it is possible that albuterol could be given at home (similarly to oral antihistamines and corticosteroids), we included albuterol because it represents treatment of acute respiratory symptoms that often accompany anaphylaxis. We acknowledge that if a less inclusive definition was used, our proportion of inpatient interventions would have been even less frequent (similar to earlier studies (8,9)).

In summary, we report that significant inpatient interventions were infrequent during pediatric FIA hospitalizations, and that asthmatic patients were more likely to require interventions. With the rising prevalence of food allergy in children, it is crucial to continue to examine FIA management to inform our progression towards an evidence-based identification of those anaphylaxis patients who truly require hospitalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	confidence interval
ED	emergency department
FIA	food-induced anaphylaxis
IQR	interquartile range
OR	odds ratio

Clinical Implications

Inpatient interventions are infrequent during pediatric hospitalizations for food-induced anaphylaxis; children with asthma were more likely to require significant therapy.

Table 1

Inpatient treatments received by children hospitalized with food-induced anaphylaxis.

	n=100
Any stay in ICU[†] (%) (*n=1 missing*)	7 (7%)
Received oxygen (%)[‡] (*n=1 missing*)	4 (4%)
Ventilator support needed (%) (*n=1 missing*)	0 (0%)
IV fluid resuscitation (fluid bolus) (%) (*n=1 missing*)	2 (2%)
Vasopressors (%) (n=1 missing)	0 (0%)
Epinephrine	
IM	3 (3%)
IV	2 (2%)
Antihistamines (%) (*n=2 missing*)	76 (78%)
Diphenhydramine (%)	65 (66%)
Other H1-blockers (%)	7 (7%)
H2-blockers (%)	46 (46%)
Corticosteroids (%) (*n=1 missing*)	68 (68%)
Prednisone/prednisolone (%)	42 (42%)
Methylprednisolone (%)	24 (24%)
Other (%)	2 (2%)
Inhaled Beta-agonists (%) (*n=2 missing*)	12 (12%)
Inhaled racemic epinephrine (%) (*n=1 missing*)	1 (1%)
Additional medications (%) (*n=1 missing*)	11 (11%)
IV terbutaline (%)	1 (1%)
IV magnesium (%)	0 (0%)
Leukotriene modifier (%)	3 (3%)
Zofran (%)	1 (1%)
Other (%)	7 (7%)
Patients receiving significant inpatient intervention[§] (%)	16 (16%)
Hospital discharge	
Hospital length of stay (days), median (IQR) (*n=1 missing*)	1 (1 – 1)
≤1 day	91 (92%)
>1 day	8 (8%)
Self-injectable epinephrine prescribed (%) (*n=2 missing*)	87 (89%)
Documentation patient taught how to use self-injectable epi (%)	38 (44%)
Hospital discharge instructions include	
Referral to an allergist (%) (*n=2 missing*)	35 (36%)
Instructions for avoidance of offending allergen (%) (n= 3 missing)	47 (48%)
Discharge diagnosis includes term “anaphylaxis” (%) (*n=4 missing*)	68 (71%)
Antihistamines prescribed (%) (*n=3 missing*)	64 (66%)
Corticosteroids prescribed (%) (*n=3 missing*)	61 (63%)
Other medications prescribed (%) (*n=3 missing*)	22 (23%)
Documentation of subsequent acute health care visits for food allergy in next year (%) (*n=1 missing*)	19 (19%)

	n=100
Number of visits, median (IQR)	1 (1 – 2)

ICU, intensive care unit; IV, intravenous; IQR denotes interquartile range

[†] All seven children had an ICU stay of one day.

[‡] Two children received oxygen via nasal cannula. Two were missing route of delivery.

[§] Defined as inpatient treatment with 1) epinephrine, 2) a significant respiratory intervention (i.e. inhaled albuterol, inhaled racemic epinephrine or respiratory support including oxygen delivery or intubation) or 3) a significant cardiovascular intervention (i.e. use of vaso-pressors or IV fluid resuscitation).

Table 2

Characteristics of children admitted to the hospital with food-induced anaphylaxis, according to significant inpatient intervention.*

	No intervention (n=84)	Received intervention (n=16)	*P* value
Demographic characteristics			
Age, median (IQR)	2.6 (1.3 – 9.5)	8.4 (5.5 – 15.0)	0.01
Male (%)	55 (65%)	12 (75%)	0.57
White race (%)	66 (79%)	8 (50%)	0.03
Medical history			
Known allergy to offending allergen (%)	33 (39%)	11 (69%)	0.052
Known allergic problems (%)	62 (74%)	15 (94%)	0.11
Prior allergic reaction to other sources (%)	24 (39%)	9 (60%)	0.16
Asthma (%)	26 (42%)	13 (87%)	0.003
Hayfever (%)	15 (24%)	6 (40%)	0.33
Atopic dermatitis (%)	27 (44%)	3 (20%)	0.14
Hives (%)	1 (2%)	0 (0%)	1.00
Angioedema (%)	0 (0%)	0 (0%)	--
Other (%)	3 (5%)	0 (0%)	1.00
Patient owns self-injectable (%) (*n=7 missing*)	30 (37%)	9 (75%)	0.03
Other chronic medical problems (%)	18 (21%)	6 (38%)	0.20
Chronic medications (%)	39 (46%)	12 (75%)	0.06
Current Reaction			
Specific food trigger causing current reaction			
Peanuts (%)	27 (32%)	4 (25%)	0.77
Tree nuts (%)	27 (32%)	1 (6%)	0.04
Seeds (%)	0 (0%)	0 (0%)	--
Fruits and vegetables (%)	2 (2%)	0 (0%)	1.00
Shellfish (%)	3 (4%)	3 (19%)	0.050
Fish (%)	0 (0%)	1 (6%)	0.16
Milk products (%)	16 (19%)	4 (25%)	0.73
Eggs (%)	6 (7%)	0 (0%)	0.59
Wheat (%)	0 (0%)	0 (0%)	--
Other food (%)	9 (11%)	3 (19%)	0.40
Location of exposure (%) (*n=7 missing*)			0.67
Home	53 (66%)	8 (62%)	
School/daycare	6 (8%)	1 (8%)	
Restaurant	2 (3%)	1 (8%)	
Other	19 (24%)	3 (23%)	
Symptom onset (%) (*n=20 missing*)			1.00
<1 hr	30 (44%)	5 (42%)	
1-3 hrs	29(43%)	6(50%)	
4-6 hrs	5 (7%)	0 (0%)	

	No intervention (n=84)	Received intervention (n=16)	*P* value
7-12 hrs	0 (0%)	0 (0%)	
>12 hrs	4 (6%)	1 (8%)	
Route of exposure			
Oral (%)	84 (100%)	15 (94%)	0.16
Skin contact (%)	1 (1%)	0 (0%)	1.00
Inhalation (%)	0 (0%)	1 (6%)	0.16
Other (%)	0 (0%)	0 (0%)	--
Prehospital/ED organ systems involved in allergic reaction			
Respiratory (%)	67 (80%)	16 (100%)	0.07
Cutaneous (%)	82 (98%)	15 (94%)	0.41
Gastrointestinal (%)	55 (65%)	15 (94%)	0.03
Cardiovascular (%)	9 (11%)	1 (6%)	1.00
Other (%)	15 (18%)	3 (19%)	1.00
Treatments			
Pre-ED treatments			
Diphenhydramine (%)	49 (78%)	10 (71%)	0.73
Other antihistamines (%)	2 (3%)	1 (7%)	0.46
Steroids (%)	12 (19%)	5 (36%)	0.28
Intravenous fluids (%)	3 (5%)	0 (0%)	1.00
Inhaled Beta-agonists (%)	10 (16%)	5 (36%)	0.13
Oxygen (%)	9 (14%)	1 (7%)	0.68
Number pre-ED epinephrine doses (%)			0.30
0	50 (60%)	6 (38%)	
1	31 (37%)	10 (63%)	
2+	3 (3%)	0 (0%)	
ED treatments			
Diphenhydramine (%)	51 (65%)	8 (53%)	0.41
Other antihistamines (%)	41 (52%)	7 (47%)	0.71
Steroids (%)	72 (91%)	12 (80%)	0.20
Intravenous fluids (%)	36 (46%)	8 (53%)	0.58
Inhaled Beta-agonists (%)	39 (49%)	10 (67%)	0.27
Oxygen (%)	7 (9%)	1 (7%)	1.00
Inhaled ipratropium (%)	13 (15%)	6 (38%)	0.12
Inhaled racemic epinephrine (%)	8 (10%)	2 (13%)	0.86
Anti-pyretics (%)	5 (6%)	1 (6%)	1.00
Anti-emetics (%)	4 (5%)	2 (13%)	0.44
Number ED epinephrine doses (%)			0.37
0	33 (39%)	5 (31%)	
1	42 (50%)	7 (44%)	
2+	9 (11%)	4 (25%)	
2+ doses of epinephrine before hospital admission (pre-ED/ED) (%)	23 (32%)	7 (44%)	0.35

	No intervention (n=84)	Received intervention (n=16)	*P* value
Symptoms consistent with anaphylaxis[†] during hospitalization	6 (7%)	2 (13%)	0.61

IQR denotes interquartile range; ED, emergency department.

[*] Defined as inpatient treatment with 1) epinephrine, 2) a significant respiratory intervention (i.e. inhaled albuterol, inhaled racemic epinephrine or respiratory support including oxygen delivery or intubation) or 3) a significant cardiovascular intervention (i.e. use of vaso-pressors or IV fluid resuscitation).

[†] Anaphylaxis defined as signs/symptoms documented in the medical record that included involvement of two or more organ systems or hypotension based on the 2011 NIAID/FAAN guidelines.