subject follow-up data. The Mann–Whitney *U* test was used to compare the median time of first epinephrine administration for critical patients before and after implementation of the new clinical pathway. A *P* value ≤.05 was considered statistically significant.

RESULTS. A 60% reduction from baseline ($P < .0001$) was noted for anaphylaxis-related admissions; 106 of 182 cases (58.2%) required admission before the pathway revision, compared with 65 of 257 (25.3%) after. No statistically significant difference was noted in the rate of patients returning to the ED within 72 hours for recurrence of anaphylaxis-related symptoms (1.3% baseline versus 2.6% after revision; $P = .99$). The median time to first epinephrine administration for critical patients before the pathway change was 15 minutes. After pathway revision, it decreased to 10 minutes, which met the target goal of <20 minutes. The target goal of >80% of discharged patients leaving with personal epinephrine auto-injectors was also met; 164 of 192 (85.4%) patients filled or received auto-injectors. In regard to safety, there were no deaths during the study period. There were no ICU admissions. Postrevision, a greater proportion of patients were seen for allergy and/or immunology follow-up (113 of 182 [62.1%] before and 166 of 257 [64.6%] after, respectively).

CONCLUSIONS. The study authors concluded that the revised clinical anaphylaxis pathway improved patient care by reducing the anaphylaxis-related admission rates, ensuring prompt delivery of epinephrine to critical patients, and increasing epinephrine auto-injector carriage rates for discharge patients. Future directions include evaluating sustainability of the updated pathway and improving efficiency of care delivery.

REVIEWER COMMENTS. This quality improvement initiative improved management of anaphylaxis in a pediatric ED. Anaphylaxis is a life-threatening event, and prompt treatment with epinephrine is vital. By reducing the observation period, the study authors demonstrated that the rate of anaphylaxis-related admissions could be reduced. This study was performed at a large tertiary-care pediatric hospital, which is a limitation; however, a similar endeavor could be performed at a smaller community hospital as well. For patient populations living in resource-poor areas, prompt recognition and treatment of anaphylaxis could mitigate prolonged ED observation periods, admissions, and prevent unnecessary transfers to tertiary-care centers. The authors of this study reiterate the importance of good provider education regarding the recognition and prompt treatment of anaphylaxis with epinephrine. It is impressive that >80% of their subjects were discharged with an epinephrine auto-injector in hand. The price of auto-injectors makes them cost prohibitive for some families despite insurance coverage. Finding ways, as this study has shown, to improve access to epinephrine is important as well.

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Further Evaluations of Factors That May Predict Biphasic Reactions in Emergency Department Anaphylaxis Patients

Lee S, Peterson A, Lohse CM, Hess EP, Campbell RL. *J Allergy Clin Immunol Pract*. 2017;5(5):1295–1301

PURPOSE OF THE STUDY. To evaluate variables to help in the identification of patients who are at an increased risk for biphasic anaphylactic reactions in the emergency department (ED).

STUDY POPULATION. The study included 807 patients in the ED with a total of 872 ED visits for anaphylaxis. The median age was 34 years, with 58% female patients and 26% pediatric subjects <18 years of age. Food was the most common inciting trigger in 35% of patients, followed by drugs in 20% of patients and venom in 12% of patients; 22% of patients had an unknown trigger. At least 1 dose of epinephrine was administered in 54% of visits, and 90% of patients received systemic steroids.

METHODS. This was an observational study of patients presenting to an academic ED from 2008 to 2015. Anaphylaxis cases were identified both retrospectively and prospectively on the basis of diagnostic criteria from the National Institute of Allergy and Infectious Diseases Food Allergy and Anaphylaxis Network. Biphasic reactions were defined as recurrent symptoms and signs of anaphylaxis occurring within 72 hours of the initial reaction without reexposure to the offending trigger.

RESULTS. There were 36 visits (4.1%) that resulted in biphasic anaphylaxis, with a median time from the initial reaction of 3 hours (range: 0.5–44 hours). Of those, 17 visits (47%) required treatment with epinephrine. The use of steroids was not associated with biphasic anaphylaxis. Statistically significant variables included a history of anaphylaxis (odds ratio [OR]: 2.74; 95% confidence interval [CI]: 1.33–5.63), an unknown trigger (OR: 2.4; 95% CI: 1.14–4.99), and delayed administration of the first epinephrine dose 60 minutes after symptom onset (OR: 2.29; 95% CI: 1.09–4.79). The risk of a biphasic reaction was 1.6% in patients with none of these risk factors and 20% in patients with all 3 risk factors.

CONCLUSIONS. The authors of this study report a rate of biphasic anaphylactic reactions of 4.1%, with almost half requiring treatment with epinephrine, indicating clinically

significant reactions. A prediction model used to assist in identifying the risk of biphasic reactions was developed.

REVIEWER COMMENTS. The current guidelines on anaphylaxis management from the Joint Task Force on Practice Parameters recommends an observation period of 4 to 8 hours. Further validation of risk factors for biphasic anaphylaxis would assist ED clinicians in customizing the length of optimal observation for individual patients. Of note, in this study, the need for prompt treatment of anaphylaxis with epinephrine is reinforced. The role of steroid treatment in the prevention of biphasic anaphylaxis remains undetermined and will require prospective trials involving a larger sample size.

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Aspirin Is an Enhancing Factor for Food-Dependent Exercise-Induced Anaphylaxis in Children

Motomura C, Matsuzaki H, Ono R, et al. *Clin Exp Allergy*. 2017;47(11):1497–1500

PURPOSE OF THE STUDY. To determine the effect of aspirin on challenge tests for food-dependent exercise-induced anaphylaxis (FDEIA) and food allergies with and without exercise in children who are suspected of having FDEIA on the basis of medical histories.

STUDY POPULATION. Pediatric patients from the outpatient clinic of the department of pediatrics at Fukuoka National Hospital were recruited between 2006 and 2015. Inclusion criteria included age <18 years, no history of drug allergies, and all patients had experienced more than a single episode of anaphylaxis after exercise. Recruitment resulted in 51 children (38 boys and 13 girls, age 4–16 years, median age 11 years).

METHODS. Patients were instructed to discontinue antihistamines 3 to 7 days before the challenge. The exercise challenge started 30 minutes after food ingestion and was standardized to 30 minutes of aerobic exercise followed by 6 minutes of anaerobic exercise. The goal heart rate was 80% of the child's maximum predicted heart rate. On day 1 of the study, patients underwent a causal food and exercise challenge by using an ergometer or treadmill. On day 2 of the study, patients underwent aspirin and causal food. On day 3 of the study, patients underwent aspirin, causal food, and exercise. Aspirin dosing was 10 mg/kg up to a maximum of 500 mg and was administered 30 minutes before food intake. Patient's history and results of serum specific immunoglobulin E levels and skin prick testing determined causal food. None of the patients had reactions to the causal food by itself. Outcomes were recorded as objective symptoms, including urticaria, cough, dyspnea, edema, nausea, vomiting, and shock. The challenge was considered positive when patients exhibited any one of these symptoms. Severe reactions resulted in termination of the challenge and appropriate treatment.

RESULTS. Out of the 51 patients, 26 had allergic reactions during at least 1 of the 3 challenge scenarios (21 boys, 6–16 years, median age of 13 years). Challenge-positive symptoms included urticaria in 21 cases (81%), cough and wheeze in 14 cases (54%), angioedema in 7 cases (27%), shock in 3 cases (12%), and nausea and vomiting in 2 cases (8%). The foods responsible for positive FDEIA reactions were shrimp in 35% ($n = 9$), wheat in 27% ($n = 7$), milk in 15% ($n = 4$), and peach, orange, sesame seed, onion, and fish in the remaining challenges. In the food-and-exercise-only challenges, allergic reactions occurred for 14 (54%) of the 26 patients. Two patients reacted with aspirin and causal food without exercise. In the challenge group with all 3 cofactors, all 26 patients experienced symptoms. This was statistically significant in the positive rates of the test when pretreated with and without aspirin ($P < .01$).

CONCLUSIONS. Pretreatment with aspirin increased the frequency and severity of allergic reactions during challenges with causal food and exercise in pediatric patients with suspected FDEIA.

REVIEWER COMMENTS. In this study, the researchers demonstrate aspirin can enhance the allergic reaction in FDEIA in the pediatric population. Similar findings have previously been demonstrated in adult studies. The mechanisms for this augmented effect are thought to be twofold. First, it is felt that aspirin in conjunction with exercise increases the amount of food antigens absorbed in the intestines. Additionally, aspirin accelerates histamine release from mast cells in patients with FDEIA. Both aspirin and nonsteroidal anti-inflammatory drugs inactivate the cyclooxygenase enzyme, and nonsteroidal anti-inflammatory drugs in adults have also been shown previously to act as a third cofactor with food and exercise, triggering FDEIA. For several years, it has been recommended that aspirin should be avoided in children age <12 years because of the risk of Reye syndrome. Because of these concerns, aspirin use in US children is uncommon. It is suggested in the findings of this study that adding aspirin to pediatric exercise challenge protocols may be useful when food and exercise fail to produce symptoms and may reduce the rate of false-negative challenges. When obtaining histories from pediatric patients with FDEIA, possible medication cofactors should be explored.

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Further Evaluations of Factors That May Predict Biphasic Reactions in Emergency Department Anaphylaxis Patients

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