Topic:
The main focus of this journal club was to 1) better define criteria to diagnose anaphylaxis; 2) update effective therapies for allergic reactions; and 3) examine the true incidence of biphasic allergic reactions.

Grading of Evidence:
The U.S. Preventive Services Task Force for ranking evidence about the effectiveness of treatments or screenings is used in this report.

- Level I: Evidence obtained from at least one properly designed randomized controlled trial.
- Level II-1: Evidence obtained from well-designed controlled trials without randomization.
- Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Articles Reviewed:
Histamine antagonists in the treatment of acute allergic reactions

Study objective:

We compared the efficacies of cimetidine (an H2-receptor antagonist) and diphenhydramine (an H1-receptor antagonist) alone and in combination for alleviation of symptoms of acute allergic reactions.

Methods:

In this prospective, randomized, double-blind study, patients and examiners assessed the severity of symptoms and signs of acute allergic reactions using a visual-analog scale before treatment and 30 minutes after treatment with 300 mg IV cimetidine and placebo, 50 mg IV diphenhydramine and placebo, or diphenhydramine plus cimetidine. Thirty-nine patients with acute allergic reactions presenting to two emergency departments of teaching hospitals.

Results:

Of the 35 patients with pruritus, all 12 receiving diphenhydramine placebo had clinically significant relief compared with six of ten (60%) receiving cimetidine plus placebo (P = .03). Twelve of 13 (92%) receiving diphenhydramine plus cimetidine had relief, which was not a significant difference from the single drugs. Comparison of mean differences in pretreatment and post-treatment symptom scores (relief scores) among groups of patients with pruritus detected significantly more relief in the group receiving diphenhydramine plus placebo (80.3 +/- 7.4) than in those receiving cimetidine plus placebo (48.8 +/- 13.4) (P = .022). Of the 33 patients with urticaria, five of 11 (46%) receiving diphenhydramine plus placebo had clinically significant relief compared with eight of ten (80%) receiving cimetidine plus placebo (P = .18). Eleven of 12 patients (92%) receiving diphenhydramine plus cimetidine had relief, which is a significant difference from those receiving diphenhydramine plus placebo (P = .027). Comparison of mean relief scores in patients with urticaria detected significantly more relief in the group receiving diphenhydramine plus cimetidine (55.3 +/- 6.5) than in the group receiving diphenhydramine plus placebo (30.7 +/- 6.1) (P = .006).

Conclusion:

For treatment of pruritus from acute allergic reactions, diphenhydramine is more effective than cimetidine, and the combination offers no
additional benefit. For treatment of acute urticaria, the combination of cimetidine and diphenhydramine is more effective than diphenhydramine alone.

Level of Evidence: I

Summary Comments:

This is a small, well-designed prospective study. Minor allergic symptoms (e.g. puritis only) responded well to H1-receptor antagonist agents alone. More significant allergic reactions (e.g. urticaria) were more effectively treated with combination H1- and H2-receptor antagonist agents.

Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists

Study objective:

Although the addition of H(2) blockers to H(1) antagonists has been promoted for use in anaphylaxis, there have been no large studies establishing the advantage of this approach in treating acute allergic syndromes. In this study we tested the hypothesis that combined H(1) and H(2) blockage results in improved outcomes in patients treated for acute allergic syndromes compared with treatment with H(1) blockade alone.

Methods:

In a randomized, double-blind, placebo-controlled trial, 91 adult patients with acute allergic syndromes were treated with either 50 mg of diphenhydramine and saline solution (control group) or with 50 mg of diphenhydramine and 50 mg of ranitidine (active group). These patients were treated with parenteral administration. Patients were recruited from an emergency department at an urban academic medical center. The primary endpoints were resolution of urticaria, angioedema, or erythema at 2 hours after protocol treatment. Areas of cutaneous involvement, heart rates, blood pressures, respiratory findings, and symptom scores were also assessed at baseline, 1 hour, and 2 hours.

Results:
There were significantly more patients without urticaria at 2 hours among the patients in the active group compared with those in the control group. Both groups had similar proportions of urticaria at baseline. Logistic regression models to predict resolution of urticaria, which accounted for baseline urticarial involvement, showed odds ratios in favor of the active group treatment. Similar findings were observed when the absence of both urticaria and angioedema was considered as the dependent variable. There was not a significant difference between the 2 groups with regard to the absence of erythema or angioedema (irrespective of the presence of urticaria) at 2 hours. Blood pressure and symptoms did not show differences between the 2 groups over time. Lower heart rates were observed 1 hour after treatment in the active treatment group (mean reduction 10 beats/min) compared with those found in the placebo group (mean reduction 6 beats/min).

**Conclusion:**

These data show that adding H(2) blockers to H(1) antagonists results in additional improvement of certain cutaneous outcomes for patients presenting with acute allergic syndromes. These findings favor the recommendation for using combined H(1) and H(2) antihistamines in acute allergic syndromes.

**Level of Evidence:** I

**Summary Comments:**

This is a small, well-designed prospective study. Minor allergic symptoms (e.g. pruritis only) responded well to H1-receptor antagonist agents alone. More significant allergic reactions (e.g. urticaria) were more effectively treated with combination H1- and H2-receptor antagonist agents.

**Incidence of Clinically Important Biphasic Reactions in Emergency Department Patients With Allergic Reactions or Anaphylaxis**


**Study objective:**

Allergic reactions are common presentations to the emergency department (ED). An unknown proportion of patients will develop biphasic reactions, and patients are often monitored for prolonged
periods to manage potential reactions. We seek to determine the incidence of clinically important biphasic reactions.

Methods:

Consecutive adult patients presenting to 2 urban EDs with allergic reactions during a 5-year period were identified. Encounters were dichotomized as “anaphylaxis” or “allergic reaction” with an explicit algorithm. A comprehensive chart review was conducted on each index and all subsequent visits to detail patient presentations, comorbidities, ED management, and predefined clinically important biphasic reactions. Regional and provincial databases were linked to identify subsequent ED visits and deaths within a 7-day period. The primary outcome was the proportion of patients with a clinically important biphasic reaction, and the secondary outcome was mortality.

Results:

Of 428,634 ED visits, 2,819 (0.66%) encounters were reviewed (496 anaphylactic and 2,323 allergic reactions). Overall, 185 patients had at least 1 subsequent visit for allergic symptoms. Five clinically important biphasic reactions were identified (0.18%; 95% confidence interval [CI] 0.07% to 0.44%), with 2 occurring during the ED visit and 3 postdischarge. There were no fatalities (95% CI 0% to 0.17%). In the anaphylaxis and allergic reaction groups, clinically important biphasic reactions occurred in 2 patients (0.40%; 95% CI 0.07% to 1.6%) and 3 patients (0.13%; 95% CI 0.03% to 0.41%), respectively.

Conclusion:

Among ED patients with allergic reactions or anaphylaxis, clinically important biphasic reactions and fatalities are rare. Our data suggest that prolonged routine monitoring of patients whose symptoms have resolved is likely unnecessary for patient safety. Ann Emerg Med 2014;63:736-744

Level of Evidence: II-2

Summary Comments:

This large retrospective study adds to the literature that indicates true biphasic allergic reactions are exceedingly rare. Detailed review of the five cases that they categorize as biphasic reactions suggests that only two were actually biphasic.
**Supplemental Educational Materials:**

Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients


**Background:**

Diagnostic criteria were proposed at the Second Symposium on the Definition and Management of Anaphylaxis convened by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN). Validation is needed before these criteria can be widely adapted into clinical practice.

**Objective:**

Our aim was to retrospectively assess the diagnostic accuracy of the NIAID/FAAN criteria for the diagnosis of anaphylaxis in emergency department (ED) patients.

**Methods:**

A retrospective cohort study of ED patients presenting from April to October 2008 was conducted. Patients given a diagnosis of an allergic reaction or anaphylaxis and a subset of patients with related diagnoses were included. Electronic medical records were reviewed and data were abstracted to determine whether the NIAID/FAAN criteria were met. Records were also independently reviewed in a blinded fashion by 2 experienced attending allergists. Final diagnosis by allergists was considered the reference standard.

**Results:**

Of 214 patients, 86 (40.2%) met the NIAID/FAAN criteria for anaphylaxis. Allergists gave 61 (28.5%) patients diagnoses of anaphylaxis, 59 (96.7%) of whom satisfied the NIAID/FAAN criteria. The interrater agreement between allergists was substantial ($\kappa = 0.77$). The test characteristics of the NIAID/FAAN criteria were as follows: sensitivity, 96.7% (95% CI, 88.8% to 99.1%); specificity, 82.4% (95% CI, 75.5% to 87.6%); positive predictive value, 68.6% (95% CI, 58.2% to 77.4%); negative predictive value, 98.4% (95% CI, 94.5% to 99.6%); positive likelihood ratio, 5.48; and negative likelihood ratio, 0.04.
Conclusions:

These results suggest that the NIAID/FAAN criteria are highly sensitive but less specific and are likely to be useful in the ED for the diagnosis of anaphylaxis.

Summary Teaching Points (STP):

**STP 1: Evidence rated Level I**
Minor allergic symptoms (e.g. puritis only) respond well to H1-receptor antagonist agents alone. More significant allergic reactions (e.g. urticaria) are more effectively treated with combination H1- and H2-receptor antagonist agents.

**STP 2: Evidence rated Level II-2**
True biphasic allergic reactions are exceedingly rare. Prolonged observation of patients whose allergic symptoms and signs have improved is not indicated.