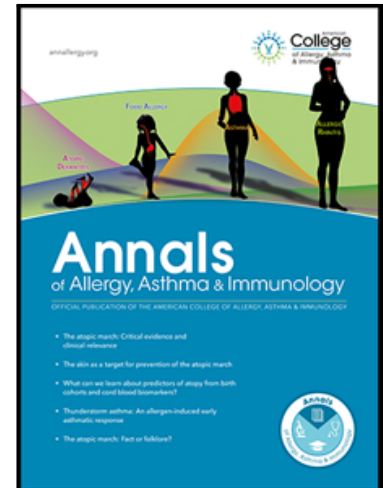


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Peanut anaphylaxis in 2022 - Decoupling epinephrine usage from emergency department evaluation

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Title

Peanut anaphylaxis in 2022 - Decoupling epinephrine usage from emergency department evaluation

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Conflict of Interest

Dr. Winslow and Dr. Gilmore report no disclosures. Dr. Kim reports advisory board membership, consultancies, and grant funding as listed below.

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Keywords

Biphasic anaphylaxis; anaphylaxis; food allergy; peanut allergy; healthcare utilization; epinephrine; COVID-19; emergency department; emergency room

Abbreviations

DBPCFC – Double-blind placebo-controlled food challenge

ED – Emergency Department

EMS – Emergency Medical Services

IQR – Interquartile range

IRB – Institutional Review Board

OR – Odds ratio

SPT – Skin prick test

US – United States

Word Count

1200

Figures

None

Tables

1

The US surpassed 54,000,000 total cases of COVID-19 by the end of 2021¹. During early pandemic contingency planning, recommendations were published advising the suspension of routine ED usage following home treatment of anaphylaxis responding to a single dose of epinephrine provided symptoms promptly resolve without recurrence². Shortly thereafter, a detailed anaphylaxis management algorithm tailored to at-home management during the COVID-19 pandemic was published³. These adaptations were devised with the goal for more selective healthcare utilization, so as to minimize risk of COVID-19 acquisition and to avoid overburdening healthcare facilities. An important underpinning for these guidelines is the perceived low risk to initial home observation after successfully treated anaphylaxis, on the basis of simulated economic modeling for peanut-triggered anaphylaxis⁴. Though the extent to which such adapted guidelines are currently in use by allergy providers remains unclear, each successive wave of SARS-CoV-2 has continued to heighten the importance of critical analysis of reflexive healthcare utilization practices for the management of anaphylaxis.

A rationale for post-reaction monitoring in the ED is the rapid detection and management of biphasic anaphylaxis. Yet, biphasic reactions are rare (0.18-14.7% of anaphylaxis events) and possibly trigger-specific⁵. When food is implicated as a trigger for anaphylaxis, Lee, *et al* reported in 2015 a protective effect for biphasic anaphylaxis (OR 0.62, [0.4-0.94])⁶, though this was not re-demonstrated in a recent analysis (OR 0.89, [0.68-1.17])⁵. To explore this question in the context of revised definitions of anaphylaxis⁷, we obtained IRB approval and retrospectively reviewed data from our clinical research center from 2011-2017. Our cohort involved highly peanut allergic children (median 4.5 years of age) previously unexposed to investigational drug or food immunotherapy who participated in 113 DBPCFCs to peanut to determine eligibility for entry into clinical trials. All participants were required to have a clinical history of peanut allergic reaction and evidence of sensitization or high titer sensitization if no history of peanut ingestion. Participants then underwent peanut DBPCFC to confirm allergy and establish the baseline threshold. Background characteristics, DBPCFC details, and exclusion criteria are displayed in Table 1. Each of the entry oral food challenges analyzed were positive, while 44 challenges (39%) resulted in a diagnosis of anaphylaxis via NIAID/FAAN criteria, and just 1 challenge (0.9%) met criteria for biphasic anaphylaxis (Table 1). Epinephrine was administered promptly for anaphylaxis treatment, with a median time 5 minutes [IQR 0-12 minutes] after applicable symptom onset. No cases of persistent or refractory anaphylaxis were identified.

Even among the *most* highly peanut sensitized children with large peanut SPT wheal size, markedly elevated levels of peanut sIgE, and in the majority of cases a prior reaction history, it is most telling that biphasic anaphylaxis events were not observed at a clinically significant frequency. Our data are strengthened by the rich clinical trial setting which provides precise symptom chronology, rigorous objective and subjective symptom criteria, and post-challenge adverse event data unavailable to outpatient or ED settings. By reporting our experiences, we hope to increase the adoption of targeted recommendations designed to reduce reliance on healthcare utilization after anaphylaxis is successfully treated among patients for whom no risk factors for biphasic anaphylaxis (e.g., severe initial presentation,

> 1 dose of epinephrine for initial management) or barriers to home observation (e.g. unavailability of adult trained in rendering post-reaction care, additional doses of epinephrine, or access to ED or EMS care) are identified.

Despite an emerging sentiment that routine ED visits are not necessary in all cases of successfully treated anaphylaxis, many resources continue to endorse this approach. Anaphylaxis management plans, for example, advise 4 hours of observation in the emergency room after epinephrine is used for the treatment of anaphylaxis, even if symptoms resolve. These management plans are widely circulated throughout clinics, childcare centers, and schools, and may deserve a closer look in the context of revised approaches to post-reaction care.

An important consideration is that the safety-driven yet reflexive coupling between epinephrine administration and subsequent ED utilization may paradoxically *reduce* epinephrine usage, by presenting unexpected obstacles to some patients. For example, patients prone to minimizing symptom severity (particularly those already subject to a variety of stressors) may justify epinephrine non-usage during reactions when epinephrine usage is warranted, to avoid a required trip to the ED following deployment of epinephrine. Recent publications identify this barrier to epinephrine usage, citing avoidance of the ED during the COVID-19 pandemic as a factor in up to 20% of anaphylaxis cases in which epinephrine is not used^{8,9}. This effect is likely to be observed during cases in which anaphylaxis symptoms are mild or subjective and when caregivers are inexperienced in recognizing symptoms or fearful of epinephrine self-administration. Additionally, such an effect may be disparately observed among those patients already burdened by certain socioeconomic determinants of health including financial strain, possibly widening healthcare disparities. Consequences of delay or omission of epinephrine during anaphylaxis treatment include a prolonged duration of symptoms as well as biphasic anaphylaxis, outcomes which *are* likely to ultimately require ED evaluation, despite the patient's original goals. Though this effect needs additional

characterization, it may contribute to the well-described suboptimal rates of home epinephrine usage among patients experiencing anaphylaxis.

The COVID-19 pandemic provided the original impetus for a number of urgently needed changes across healthcare systems. Ad hoc changes in practice were adapted to normalize the decision to continue anaphylaxis observation at home, provided both treatment and response are timely and appropriate. These changes have accelerated an evolution to precision-based anaphylaxis management, though the safety implications resulting from these changes are poorly established. We would like to contribute further support to the low rate of biphasic anaphylaxis, by submitting our center's experience with a high-risk peanut allergy cohort undergoing entry oral food challenge. Our research observations are limited by the exclusion of patients at entry who have previously experienced an episode of severe anaphylaxis and by the infrequent occurrence of biphasic anaphylaxis during DBPCFC which may each reduce generalizability. However, our work importantly highlights that elevations in biomarkers for allergic sensitization to peanut are not independently predictive of food-triggered biphasic anaphylaxis. While the setting of controlled clinical research as we have suggested may be ideal to precisely convey symptom chronology and timing of epinephrine administration, we acknowledge that anaphylaxis outside of a medically supervised setting is not as likely to be recognized nor treated with such rapidity. Yet we are still hopeful our work may both inform future research regarding biphasic anaphylaxis and may encourage providers to make use of a more targeted approach to anaphylaxis counseling. Similar to previously recommended adaptations to anaphylaxis post-reaction care published at the onset of the pandemic^{2,3}, we encourage providers to consider selective deferral of healthcare utilization for patients experiencing food-triggered anaphylaxis who lack biphasic anaphylaxis risk factors and barriers to home observation, even among children with biomarkers reflective of high degrees of peanut sensitization. Additional investigation of DBPCFC research cohorts may be useful in providing further post-reaction follow-up data and both mechanistic and clinical insight from which more robustly defined risk factors for biphasic anaphylaxis can be derived. As providers in allergy/immunology, we are uniquely positioned

to lead the charge on providing more targeted guidance on routine care after the diagnosis of anaphylaxis, and may even be positioned to reduce reliance on emergency departments.

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Table 1

Demographic Characteristics	
N	125
Age, median years (interquartile range)	4.5 (2.5-8)
Male	74
Female	51
Caucasian	112
African American	4
Native American	2
Asian	5
Mixed	2
Medical Comorbidities	
Atopic Dermatitis	89
Asthma	51
Other Food Allergies	61
Baseline Peanut Allergy Evaluation	
Peanut sIgE, median kU _A /L (interquartile range)	61.6 (14-160)
Peanut SPT, median mm (interquartile range)	13 (9-19)
Entry DBPCFC Characteristics for Study Participants	
PnOIT4 (NCT01814241)	8 doses: 1, 5, 15, 50, 75, 100, 250, 500 mg; 15-30 min increments

TLC (NCT01373242)	5 doses: 25, 50, 100, 250, 575 mg; 10-20 min increments
FARE/SLIT (NCT02304991)	6 doses: 3, 10, 30, 100, 300, 557 mg; 10-20 min increments
When symptomatic, patients were observed for 2 hours post-challenge in all studies	
Exclusion: history of severe anaphylaxis (hypotension/shock, neurologic impairment including cyanosis or hypoxemia [SpO ₂ < 92%], confusion, collapse, loss of consciousness, or incontinence)	
Biphasic Anaphylaxis DBPCFC Characteristics	
Biphasic anaphylaxis (N=1/113)	5 doses: 1, 5, 15, 50, 100 mg at 0, 10, 20, 30, 40 mins respectively; 43 mins skin rash – diphenhydramine; 55 mins GI symptoms – epinephrine, prompt resolution; 185 mins wheezing/cough – epinephrine, prompt resolution; 245 mins rash; 305 mins resolution of rash; 395 mins patient discharged

Pooled demographic information, medical comorbidities, baseline peanut allergy evaluation for study

cohort, DBPCFC characteristics, and biphasic anaphylaxis characteristics