



Editorial

Factoring in cofactors in the diagnosis and management of anaphylaxis



Anaphylaxis is the most severe manifestation of an acute allergic reaction and will occur in approximately 5% of the US population.¹ Food allergy is the most common trigger, with approximately 25% to 50% of food reactions in adults resulting in anaphylaxis.² However, even in an individual patient with food allergy, reaction severity to a known food allergen can be unpredictable and variable in severity.³ In addition, some individuals may tolerate an allergen exposure in some cases but react in others.³ This phenomenon can be partially explained by cofactors, which either increase reaction severity or lower the threshold of reactivity in an individual. Cofactors, which include exercise, various medications, and alcohol, have been identified in up to 30% of anaphylactic reactions in adults (and up to 58% of food anaphylaxis).^{2,3} In some individuals, various cofactors may be required to increase reaction severity or lower reaction threshold.³ Cofactors remain poorly understood, poorly described, and likely underrecognized.

In the current issue of the *Annals of Allergy, Asthma & Immunology*, Bartra et al² provide a comprehensive review of different extrinsic cofactors and the mechanisms (when understood) involved in alterations of food allergic reaction severity or threshold. This review focuses on exercise, nonsteroidal anti-inflammatory drugs, alcohol, angiotensin-converting enzyme inhibitors and beta-blockers, lipid-lowering drugs, estrogens, proton pump inhibitors, and sleep deprivation. This review will serve as a pertinent resource for any clinician involved in the workup of food anaphylaxis. Although the authors discuss each cofactor independently, they rightly note that a patient may “even need more than one cofactor to develop a more severe reaction ... while either cofactor in isolation may not be needed” to trigger a reaction.² Of note, this review focuses largely on modifiable cofactors and does not provide a comprehensive discussion on nonmodifiable (intrinsic) cofactors including age, sex, and comorbidities.⁴

This review has the potential to influence anaphylaxis diagnosis and management. It serves to remind the clinician of the importance of screening for, and evaluating, the presence of cofactors in any individual with anaphylaxis. A high degree of suspicion is necessary when evaluating cofactors as patients may not recall cofactors nor volunteer them. Cofactors may be the reason why a particular patient tolerates a food (or only has a mild reaction) in some instances, but in others has a severe allergic

reaction.⁵ Cofactors may be the reason a clinical history indicates a strong suspicion of a reaction to a specific food allergen but then there is a negative oral food challenge result.⁶ In that scenario, a food challenge in the presence of a cofactor could be considered. Cofactors should also be kept in mind for anaphylaxis long-term management. In many cases, such as with medications and alcohol use, cofactors are modifiable and have the potential to reduce severe anaphylaxis risk among our patients.

This review is also a reminder to the clinician of gaps in anaphylaxis knowledge. As noted by Bartra et al,² further information elucidating the mechanism for various cofactors is necessary as many are poorly understood. An understanding of mechanisms could serve to identify possible biomarkers or prophylactic therapies for our patient population.³ As has been previously postulated, because there is an individual predisposition to cofactor-enhanced anaphylaxis and as most cofactors can influence anaphylaxis severity or threshold, there may be some similar or overlapping pathogenic mechanism.³

Studies specific to cofactors in children are also necessary, as the vast majority of studies on cofactors have been conducted in the adult population. Several cofactors, including illness and exercise (or, in a younger pediatric population, active play), warrant prompt and thorough investigation for children, especially as children are increasingly involved in food oral immunotherapy. Food-dependent exercise-induced anaphylaxis has been described among children, an observation that is of concern for children at risk of anaphylaxis, including those who are undergoing immunotherapy.⁷ Alcohol is an additional cofactor that remains minimally explored in adolescents at risk of anaphylaxis but one that warrants substantial exploration. Adolescents represent an age group that faces the combined risks of increasing rates of alcohol consumption⁸ and general risk taking. The potential for alcohol as a cofactor and the oft-parallel behavior of smoking, which may exacerbate comorbid asthma, remain poorly elucidated, but theoretically substantial, in this age group.

Finally, an additional cofactor for anaphylaxis that warrants investigation among both adults and children is gender. Although differences in estrogens, and more broadly biological sex, have been described,² there is a paucity of data on gender as a cofactor. However, as gender may predict health-related behaviors, ranging from allergen exposure to seeking health care,⁹ gender (independent of sex) may be an additional cofactor for anaphylaxis.

Moving forward, we should consider how we collect, code, and interpret anaphylaxis data. It has been previously described that anaphylaxis triggers are not coded properly in data systems which prevents the opportunity to accurately identify triggers and cofactors. Proper, standardized data collection would further

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the opportunity to study the impact of cofactors more granularly in the future.¹⁰

In conclusion, this review prompts the clinician to remain broad in the initial diagnostic workup for anaphylaxis and always consider cofactors as a contributing factor. As aptly stated at the end of this review, cofactors should always be evaluated in our patient population to reduce the risk of, and severity of, anaphylaxis.

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