

### Guidance to Patients for Anaphylaxis Management: No Blanket Approach



To the Editor:

We feel compelled to respond to the recent opinion piece by Turner et al, in the *Journal of Allergy and Clinical Immunology: In Practice*, entitled “The emperor has no symptoms: the risks of a blanket approach to using epinephrine auto-injectors for all allergic reactions.”<sup>1</sup> In their article, the authors express concern regarding “blanket” recommendations for the use of epinephrine to treat allergic reactions. They raise theoretical concerns about the potential for “too early” use of epinephrine and “slippage” in recommendations for epinephrine administration that they feel could “encourage overuse.” However, these contentions are not supported by the literature and the article contains numerous errors and misrepresentations that undermine the authors’ arguments.

Turner et al cite their own review article<sup>2</sup> to state: “our biggest challenge in the management of food-allergic individuals is in identifying those who are most at risk of severe, life-threatening reactions; although fatal anaphylaxis is rare, it is also very unpredictable.” They also remark: “The vast majority of fatal reactions (to food) are due to substantial levels of exposure accidentally ingested, often with other significant cofactors present contributing to the severity of the reaction.”<sup>3-5</sup> Together, these statements seem to support the concept of early and generalized use of epinephrine in suspected anaphylaxis, as it is unclear who will have a systemic reaction and it is difficult to predict the severity. Much of the literature points out the unpredictability of allergic reactions, particularly to food, and has concluded that epinephrine is actually underprescribed and underutilized in this situation, including in the authors’ region.<sup>6</sup>

The authors provide 2 pieces of evidence to support their contention that there is “slippage” in epinephrine prescribing for “nonsevere symptoms.” One is the Food Allergy & Anaphylaxis Emergency Care Plan (FAAECPP) developed by Food Allergy Research & Education (FARE), because of the “recommendation to administer epinephrine even in the absence of symptoms.” However, their contention is flawed as they extract one small portion of this care plan and present it out of context. The FAAECPP clearly requires the patient’s physician to recommend (check the option) that epinephrine should be given if allergen ingestion was likely or if the allergen was definitely eaten. This is not a “blanket” recommendation, but a choice to be made by the patient’s physician based on his or her knowledge and experience with the patient. The authors also leave out that the rest of the page of the FAAECPP goes on to explain severe symptoms and recommends epinephrine for mild symptoms only when more than one system area is observed. Finally, the authors state that they are “unaware of the evidence base on which some of these directives have been promulgated.” In fact, these recommendations are directly derived from the American Academy of Allergy, Asthma and Immunology’s “Anaphylaxis in schools and other childcare settings” position statement.<sup>7</sup> It states: “In patients who have had anaphylactic reactions, it is recommended that epinephrine be given at the start of any reaction occurring in conjunction with exposure to a known or suspected allergen. In situations where there has been a history of a severe cardiovascular collapse to an allergen, the physician may advocate that epinephrine be

administered immediately after an insect sting or ingestion of the offending food and before any reaction has begun. Reports have shown that adequate warning signs are not always present before serious reactions develop.” This statement alone provides a clear basis for the FAAECPP recommendations.

The second argument provided by the authors to support their “slippage” hypothesis is that this is driven by commercial considerations from autoinjector manufacturers. The only information they provide for this is “patient literature” from an epinephrine autoinjector device not approved or available in the United States.<sup>8</sup> They write, “... guidelines and patient literature should be written by non-conflicted individuals with appropriate expertise, and not driven by a marketing agenda.” The suggestion that recommendations surrounding epinephrine are based on “commercial interest” is not supported by fact as professional societies and the NIH have generated the guidelines on this topic. FARE’s recommendations come from our Medical Advisory Board, a group of independent physicians, and are based on the scientific literature and physician experience.

Research shows that fatalities caused by food-induced anaphylaxis are commonly associated with delayed use or lack of proper epinephrine dosing.<sup>9</sup> Although health care professionals can rely on published diagnostic criteria for anaphylaxis to help them understand and recognize the spectrum of symptoms that constitute anaphylaxis, this criterion is not written for the layperson. Thus, the Guidelines for the Diagnosis and Management of Food Allergy in the United States recommend individuals with food allergies have a written, individualized anaphylaxis care plan, such as the one made available by FARE. This document is necessary (and required for students with food allergies by many schools) to outline emergency treatment instructions, communicated in a manner that is easy to understand when seconds count. Deaths caused by food-induced anaphylaxis have been reported within 30 minutes to 2 hours of exposure.<sup>10</sup> Repeatedly and tragically, we have heard firsthand from grieving parents about fatal reactions that progressed quickly and in which epinephrine was not administered in a timely manner.

We all look forward to studies that can provide additional and specific guidance on whether and when to administer epinephrine. Until then, we believe that this is a decision that is highly individualized and must take place between a physician and a patient or the patient’s caregiver. This opinion piece misrepresents and simplifies this important issue, potentially placing food-allergic patients at risk and undermining confidence in their physicians.

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Conflicts of interest: J. R. Baker declares that he is employed by Food Allergy Research & Education (as the CEO and Chief Medical Officer). His organization has also received grants from Food Allergy Research & Education in support of educational and awareness activities (such as sponsorship of patient educational conferences).

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## Reply

### To the Editor:



We welcome Baker's contribution to the debate as to the use of early epinephrine to treat food-triggered allergic reactions.<sup>1</sup> However, it is unfortunate that although he asserts that our article<sup>2</sup> "contains numerous errors," he fails to bring any examples other than to discuss one small section that deals with the trend ("slippage"), as we perceive it, toward early epinephrine use. There may be geographical differences between North America and elsewhere in terms of the nuances of advice provided to patients, but routinely advising people who have no symptoms to self-inject epinephrine makes little sense to us, and there is no evidence that this practice is efficacious.

With regard to the recommendation for "early" epinephrine, we were not questioning the origin, but rather the actual evidence-base for this strategy. Baker cites the American Academy of Allergy, Asthma & Immunology (AAAAI) Position statement "Anaphylaxis in schools and other childcare settings,"<sup>3</sup> a document published 18 years ago (and includes a disclaimer that it should "not be considered to reflect current AAAAI standards or policy after five years from the date of publication"). In this statement, the suggestion to administer epinephrine before onset of any symptoms is limited to "situations where there has been a history of a severe cardiovascular collapse to an allergen." That is clearly a very different clinical scenario from that implied by the Food Allergy Research & Education (FARE) emergency plan where this is to be considered in those with previous anaphylaxis of any severity. We would suggest that this is consistent with the "slippage" we discuss in our article. Baker further cites the National Institute of Allergy and Infectious Diseases (NIAID) guidelines<sup>4</sup> as further evidence; however, it is noteworthy that the NIAID guideline does not recommend the use of epinephrine before onset of any symptoms.

We discuss in our article our concerns with regard to pre-emptive epinephrine as a treatment strategy.<sup>2</sup> No study has ever

demonstrated that epinephrine has prophylactic efficacy in the way that these options exist for hereditary angioedema or migraine. Furthermore, there is at least one case report of a patient who was repeatedly administered epinephrine during an initially mild allergic reaction, a strategy that did not prevent progression to fatal respiratory arrest.<sup>5</sup> We therefore challenge Baker's assertion that there is evidence beyond that of expert theoretical opinion that has proven pre-emptive epinephrine to be effective.

Baker is mistaken in stating: "it is unclear who will have a systemic reaction": published series (and clinical experience) demonstrate that most community reactions present with systemic features<sup>4</sup> (eg, cutaneous symptoms that occur after oral contact are, by definition, systemic and not local) yet the majority resolve without evolving into anaphylaxis. Underlying systemic immune activation is present in even mild, nonanaphylactic reactions.<sup>6</sup> It is therefore likely that the majority of food-allergic reactions have systemic involvement. What is not clear is in whom, and why, this might progress to a severe, life-threatening event<sup>7</sup>: food allergic reactions are unpredictable, a concern that rightly drives the provision of epinephrine autoinjector devices (EAI) for community use. However, one should consider that at least 50% of peanut-allergic individuals need to consume more than 100 mg protein (about half a peanut) to have any reaction at all.<sup>8</sup> In considering the current status quo regarding the use of EAI in the community, we should look to the available data: 80% of teenagers experiencing anaphylaxis in the community fail to use EAI, yet experience spontaneous resolution of their symptoms.<sup>9</sup>

This is clearly an unsatisfactory state of affairs that increases risk and needs to be addressed. How do we, as health care professionals, respond? One strategy is to recommend the use of EAI at onset of any symptoms. However, we have concerns over this approach. Reactions may be unpredictable, but they are not a one-way street to fatal outcome: successive reactions are definitely not always more severe, and fatal outcomes are fortunately rare. Fear-based rhetoric must be challenged within the food allergy community and in physician-patient dialogues across all fields of medicine. Given that many allergic individuals fail to use EAI even when experiencing pronounced respiratory symptoms,<sup>9</sup> we contend they are even less likely to use EAI for any, let alone no symptoms. Although delayed EAI has been associated with fatal outcomes, there are as many fatalities where EAI were administered in a timely manner.<sup>10,11</sup> EAI alone is insufficient to protect against death.<sup>10,11</sup> Severe anaphylaxis requires urgent intensive intervention beyond EAI.<sup>12</sup> Recognition of anaphylaxis and requesting urgent medical assistance are at least as important as EAI in preventing a fatal outcome. There is simply no evidence that pre-emptive epinephrine results in better outcomes than carefully timed and prompt use. This is our key point: no evidence.

We agree that the provision and use of EAI "is a decision that is highly individualized and must take place between a physician and a patient or the patient's caregiver." However, as reviewed by Sicherer and Simons,<sup>13</sup> health care professionals need to consider a range of issues, including indication, the importance of subsequent hospital assessment (which is a barrier to EAI use for some), and patient knowledge and ability to self-manage their food allergy including accidental reactions. Many reactions in children occur in the school environment, where staff may be unable to provide the same degree of individualized care.

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