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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.¹ However, it is unfortunate that although he asserts that our article² "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,"³ 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) guidelines⁴ 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.² 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.⁵ 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 features⁴ (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.⁶ 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 event⁷: 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.⁸ 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.⁹

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,⁹ 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.^{10,11} EAI alone is insufficient to protect against death.^{10,11} Severe anaphylaxis requires urgent intensive intervention beyond EAI.¹² 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,¹³ 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.

Unfortunately, we now need to recognize that device cost is an emerging as a significant issue for many families.¹⁴

Baker comments that FARE's recommendations come from its "Medical Advisory Board, a group of independent physicians, and are based on the scientific literature and physician experience." We are also "independent physicians"; we have read the "scientific literature" and have comparable "physician experience." We simply cannot find sufficient evidence to support this particular recommendation. Baker is backing eminence over evidence: his comment makes it clear that the disputed recommendation is based on Level D evidence, that of expert opinion.

Many families do not meet allergy specialists to discuss self-care issues or to "get" EAIs. It is our experience that many bring advice sheets such as FARE's to their family doctor or pediatrician, who presumably would need to be very sure of their reasons for not "ticking the boxes" that Baker highlights. The phraseology we have highlighted on the new FARE plan might suggest that the recommendation for early EAI use—even in the absence of symptoms—is no longer an exception (as suggested by the original AAAAI Position Statement) but the norm. Routine provision of EAI to treat all reactions—irrespective of severity and in particular, potential reactions in the absence of symptoms—is something that warrants further discussion before it can become a tick-box exercise.

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Conflicts of interest: P. J. Turner has received money for consultancy from UK Food Standards Agency. His institution has received money for consultancy from Reacta Biotech. His institution has also received grants from the Medical Research Council (research funding for studies into anaphylaxis), NIHR/Imperial BRC, EU FP7 Programme (research funding to the Integrated Approaches to Food Allergen and Allergy Risk Management (iFAAM) consortium for investigation of matrix effects on patients having food allergic reactions), and UK-Department of Health (research funding [vaccine safety and efficacy]). He has also received money for travel expenses unrelated to the activities listed on the disclosure form from the National Institute for Health and Care Excellence (receipted expenses only). Finally, he has also disclosed the following: "I have co-lead a working group of members of the British Society for Allergy and Clinical Immunology who have developed and implemented the UK National Allergy Management Plans, together with support from the Royal College of Paediatrics and Child Health, and the Patient Representative groups Allergy UK and the Anaphylaxis Campaign. No financial support was received in this work."

A. DunnGalvin has received money paid to them for board membership and consultancy from Aimmune Corporation. Her institution has also received grants (pending grants) from Aimmune Corporation, SafeFood Ireland, and an EU FP7 Programme (research funding to iFAAM consortium [WP6.1] for investigation of real-time analysis of patients having food allergic reactions in the community). J. O'B. Hourihane has received money paid to him for board membership and consultancy from Aimmune Corporation. His institution has also received grants (pending grants) from Aimmune Corporation, DBV Technologies, National Children's Research Centre in Ireland (research funding for epidemiological studies of anaphylaxis in Ireland), and an EU FP7 Programme (research funding to iFAAM consortium [WP6.1] for investigation of real-time analysis of patients having food allergic reactions in the community). He has also received payment for lectures including service on speaker's bureaus from Nutricia Ireland and Sweden (speaker's fees).

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