

# Is the Use of Epinephrine a Good Marker of Severity of Allergic Reactions During Oral Food Challenges?

Alexandra F. Santos, MD, MSC<sup>a,b</sup>, George Du Toit, MB BCH, FRCPCH<sup>a,b</sup>, and Gideon Lack, MB BCH, FRCPCH<sup>a,b</sup> London, United Kingdom

Oral food challenges (OFC) are the gold standard for the diagnosis of food allergy.<sup>1</sup> They are also the method of choice to assess the resolution of food allergies. In clinical practice, most centers use open OFC for diagnostic purposes. In the research setting, double-blind placebo-controlled food challenges (DBPCFC) are required to ensure an unbiased outcome.<sup>2</sup> In therapeutic trials for food allergy, DBPCFC are performed in patients known to be allergic and a positive outcome is expected, with potentially severe symptoms that can be life-threatening. Furthermore, patients with food allergy entering clinical research studies often have to be submitted to repeat DBPCFC to assess response to treatment.

In studies where OFC are performed to diagnose food allergy, the rate of severe reactions that require the use of epinephrine is usually low, which varies between 1.6% and 11%.<sup>3-5</sup> In this issue of the journal, Noone et al<sup>6</sup> reported a higher proportion (39.2%) of patients being treated with epinephrine in 74 positive DBPCFC performed as part of 2 therapeutic trials carried out at one center with extensive expertise in the field. Treatment with epinephrine was associated with prior need for epinephrine for allergic reactions and with the absence of asthma, but not with the previous history of anaphylaxis, food challenged, threshold dose, skin prick test, or specific IgE results.<sup>6</sup>

Depending on the center and the protocol adopted, a variety of reasons could explain the discrepancy between the severity of allergic reactions during diagnostic OFC and during research OFC. One of the reasons could be the patient selection, ie, the clinical phenotype of the patients included in the studies and undergoing OFC. Individuals with more persistent food allergy may develop more severe symptoms than patients with a transient form of food allergy.<sup>7</sup> A second possible reason could be the rigor of protocol requirements in research studies. For example, the need for objective signs for an OFC to be considered positive could lead to more severe symptoms. On the contrary, if the OFC is stopped when subjective symptoms develop, a lower dose of the allergen would be given that results in less severe reactions.<sup>8</sup> A third reason could be the use of double-blinded and placebo doses for the OFC. Allergens hidden in a matrix may be able to cause symptoms only after digestion in the gastrointestinal tract, perhaps after a time interval when a higher dose of allergen has been consumed, as opposed to open OFC that possibly allow for direct contact of the allergen with the oral mucosa and lead to the earlier recognition of allergic symptoms. The food preparation used can also play a role in the severity of allergic reactions, with higher fat content resulting in a higher cumulative dose of food protein eaten and more severe symptoms.<sup>9</sup> Additional reasons that can influence the severity of allergic reactions relate to other aspects of the OFC protocol, namely if doses are continued to be given despite the development of mild symptoms<sup>10</sup> and the interval at which challenge doses are given, with a shorter interval possibly leading to more severe symptoms.<sup>11,12</sup> Finally, the use of epinephrine could be influenced by the knowledge that a child required epinephrine in previous allergic reactions, which can increase anxiety in the patient and concerns in the assessor, and thus lead to the more prompt use of epinephrine. In the study by Noone et al,<sup>6</sup> prior need for epinephrine for allergic reactions was indeed the main factor associated with epinephrine use.

One of the difficulties in interpreting the results of OFC is discrepancies between the use of epinephrine and the severity reported. Some people equate the severity of allergic reactions to the use of epinephrine, some centers use epinephrine early and some later on, and so it is difficult to know whether the use of epinephrine is a good marker of severity of allergic reactions. Of the 74 reactions developed during the DBPCFC reported in the cited study,<sup>6</sup> 2.7% were classified as severe despite epinephrine being given to 39.2% of patients. There is no universal agreement in the criteria for administering epinephrine in the context of OFC. A delay in administering epinephrine has previously been identified as a major risk factor for fatal food-induced anaphylaxis.<sup>13</sup> In a case series of fatal food allergic reactions, only 15% of patients received epinephrine in the first hour after food ingestion.<sup>14</sup> Noone et al<sup>6</sup> reported that the median time

<sup>a</sup>Department of Pediatric Allergy, Division of Asthma, Allergy & Lung Biology, King's College, London, United Kingdom

<sup>b</sup>MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, United Kingdom

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Corresponding author: Gideon Lack, MB BCH, FRCPCH, Department of Pediatric Allergy, St Thomas' Hospital, 2nd Floor, Stairwell B, South Wing, Westminster Bridge Road, London SE1 7EH, United Kingdom. E-mail: [gideon.lack@kcl.ac.uk](mailto:gideon.lack@kcl.ac.uk).

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between the onset of symptoms and treatment with epinephrine was 65 minutes. Would the severity of challenges be lower if epinephrine were administered sooner? A total of 75% of patients with moderate reactions and 18.8% of patients with mild reactions were treated with epinephrine. Were the reactions milder because epinephrine prevented progression to more severe manifestations? This instructive report highlights the need for standardized and validated symptom score measures in clinical studies and accepted criteria for the administration of different medications, which would allow us to compare outcomes of reaction severity between different studies and, more importantly, to diminish severity. Randomized controlled trials (RCT) are needed for a better understanding of the effect of treatment in the severity of allergic reactions, namely the timing of epinephrine use and if epinephrine should be given before the onset of moderate to severe symptoms. Also the prompt administration of other medications could possibly reduce the severity of the reactions. It has long been assumed that antihistamines neither prevent nor treat anaphylaxis but only provide symptom relief, but there is no strong evidence one way or the other. RCT are required to assess the use of high-dose short- or long-acting H1-receptor antagonists in the treatment of anaphylaxis. Similarly, RCT are also needed to test the benefit of short-acting  $\beta_2$ -agonists before the development of bronchospasm in patients with a diagnosis of asthma and previous respiratory symptoms during an allergic reaction.

To be able to compare studies, it is important to ensure homogeneity of the clinical team giving treatment, including timing and level of symptoms, and also that the same severity grading system and similar food preparation and OFC protocol are used across centers. There are currently no reliable predictors of the severity of allergic reactions during OFC. The fact that OFC may unpredictably induce severe allergic reactions in any patient, to any food, even when the indication for OFC is to assess resolution of food allergy,<sup>15</sup> mandates that the attending staff are skilled in the early recognition and treatment of anaphylaxis. Simulation clinical scenarios have been successfully used in other areas of medicine to keep the clinical team up to date and prepared to deal with emergency situations and should be encouraged in the practice of Paediatric Allergy.<sup>16</sup>

In therapeutic trials, the requirement of repeated assessment of clinical reactivity in patients known to be food allergic raises concerns not only with respect to the safety of the treatment being tested but also of the method used to monitor response to treatment, ie, OFC. With the increasing number of therapeutic trials for food allergy, a better biomarker for food allergy that could be used to confirm the diagnosis of food allergy and to monitor the response to treatment over time as an alternative to OFC is desirable. Before such a biomarker is available, it remains essential to ensure that OFC are performed in specialized centers by well-trained and experienced clinical teams with resources

available to treat anaphylaxis. This is becoming progressively important in the light of increasing clinical trials used to immune-modulate food allergies, which all require DBPCFC. The early recognition and prompt treatment of allergic symptoms and signs remains central to ensuring patient safety.

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