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## Apparent lack of response to epinephrine in anaphylaxis

### To the Editor:

The paper "Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001," by Bernstein et al,<sup>1</sup> includes detailed case reports of anaphylaxis deaths in 17 patients. The information about treatment compiled in Table II of this paper includes: whether or not epinephrine was given, the time from the onset of the allergic reaction to epinephrine injection, and the epinephrine initial dose and route of administration. The importance of such careful descriptions of epinephrine use in the treatment of anaphylaxis cannot be overestimated, given the absence of prospective, randomized, controlled clinical trials of epinephrine in anaphylaxis. It appears as if 6 of the 17 patients who died either did not receive epinephrine at all (patients 2, 5, and 9), or received it 10 to >30 minutes after the reaction started (patients 1, 3, and 17). Although patient 16 received it immediately, the dose was unknown, and patient 4 received it in an unknown dose after an unknown period of time had elapsed since the onset of the reaction.<sup>1</sup>

The disconcerting fact remains that 9 of the 17 patients succumbing to anaphylaxis had received the recommended dose of epinephrine 0.3-0.5 mg, either immediately or within 3 minutes of the start of their allergic reaction.<sup>1</sup> Health care professionals place considerable faith in the efficacy of an initial 0.3-0.5 mg dose of epinephrine injected promptly in the treatment of anaphylaxis.<sup>2</sup> Availability of a body weight measurement from within a few months of death for these 9 patients might facilitate discussion about the adequacy, or lack of adequacy, of this initial 0.3-0.5 mg epinephrine dose.

In addition to the epinephrine dose injected, potential reasons for apparent lack of response to epinephrine treatment in patients with anaphylaxis from allergen injection or any other trigger include use of the subcutaneous route for epinephrine injection and the presence of asthma as a comorbidity, both of which are discussed by Bernstein et al.<sup>1</sup> There are many other possible scenarios—for example, injection of epinephrine that is past the expiry date, use of a suboptimal site of injection, and such rapid progression of anaphylaxis that no treatment avails.<sup>3</sup>

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## Reply

### To the Editor:

The recently published 12-year survey of fatal immunotherapy (IT) reactions spanning 1990-2001 is the third such study sponsored by the AAAAI.<sup>1</sup> These surveys have been very useful in stimulating physicians to closely examine circumstances associated with fatal IT-related events and provide important clinical evidence required in formulating practice guidelines. In this vein, Dr Simons has noted that although epinephrine administration was delayed or not given in 6 cases, the majority of fatal reactors for whom we were provided details of fatal events apparently were given recommended doses of epinephrine in a timely fashion ( $\leq 3$  minutes after IT injections).<sup>2</sup> Thus, in the latter cases, epinephrine was administered appropriately and according to guidelines existing during the 1990s. It is noteworthy that these events preceded more recent guidelines recommending administration of intramuscular epinephrine in the vastus lateralis, which has been shown by Dr Simons and colleagues to achieve higher plasma epinephrine levels in normal volunteer subjects.<sup>3,4</sup> Although use of the IM route is quite rational based on current evidence in normal subjects, we await future studies to see if this change in practice reduces the incidence of fatal anaphylaxis associated with allergen IT.

I agree with Dr Simons that there may be uncertainty regarding the optimal initial dose but also regarding the adequacy of giving only 1-2 doses in a refractory patient. As cited in the Discussion of our report, a recently issued British guideline recommends an initial intramuscular epinephrine dose of 0.5 mg in adult patients and repeat after 5 minutes if indicated.<sup>5</sup> The recently updated *Diagnosis and Management of Anaphylaxis: An Updated Practice Parameter*<sup>6</sup> unequivocally recommends that epinephrine dosing (0.3-0.5 mg) be repeated every 5 minutes (or sooner) to control symptoms and increase blood pressure. It is noteworthy that among those reporting total epinephrine doses in our survey, all but one patient received less than 1 mg, which begs the question whether poor responses were due to intrinsic resistance to epinephrine or inadequate total or cumulative dosages.

Finally, as Dr Simons mentions, asthma comorbidity is an apparent susceptibility factor identified in all prior surveys of IT fatalities.<sup>7-9</sup> Such observations clearly support recently issued guidelines that recommend intensive monitoring of all asthmatic individuals receiving