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## Specific IgE to gelatin as a cause of anaphylaxis to zoster vaccine



To the Editor:

Reading the recent letter from Stone et al<sup>1</sup> reminded us of a subject from our previous galactose- $\alpha$ -1,3-galactose (alpha-gal) study. Indeed, she may well be the same 76-year-old lady found in the letter (Table E1) who was reported as negative to alpha-gal. Her first reaction to meat started 45 minutes after eating barbecue, only a few months following her recovery from Lyme disease.<sup>2,3</sup> Since then she has had multiple reactions of varying severity, some of which started less than 1 hour after ingestion of red meat. Although not the average time for the onset of an alpha-gal allergic reaction, which is approximately 3 to 5 hours, her reactions to meat were not immediate either.<sup>2,4</sup> In 2007, 20 minutes after receiving zoster vaccine, she went into cardiovascular collapse, requiring emergency treatment and an overnight hospital stay. In 2010, as a subject in our alpha-gal study of late onset reactions to meat in relation to tick bites, she was tested for IgE to alpha-gal as well as various meat products. Having been found negative for IgE to alpha-gal,

with low titers to beef and chicken, she was tested for IgE to gelatins (Table I).<sup>5</sup>

Clinically, the patient described above (subject no. 1) demonstrated similar symptoms as did 4 alpha-gal–positive subjects, despite some of her reactions only being delayed by 40 minutes to 2 hours. Serologically, the other subjects had high levels of IgE to mammals containing alpha-gal, whereas our index subject was negative to alpha-gal and to most alpha-gal–related products.<sup>2</sup> In contrast, she had high titer to both bovine and porcine gelatin. In addition, she had a negative assay to Fel d 2 (cat serum albumin) and pork, serological indicators of pork-cat syndrome.<sup>6</sup> Thus, IgE results for subject number 1 eliminate both the alpha-gal syndrome and the pork-cat syndrome as the cause of her reactions to meat.

Patient number 1 brings up 2 questions:

- Was her allergy to nonprimate mammalian gelatin induced by a tick bite?
- Are there differences in the specificity of IgE to alpha-gal that explain why some patients react to zoster vaccine whereas others do not?

Stone et al remark that ImmunoCAP measurements of IgE to alpha-gal before and after incubation of sera with porcine or bovine gelatin resulted in only modest changes. By contrast, incubation of sera with vaccines containing high levels of gelatin, for example, MMR or zoster vaccine, decreased IgE titers to alpha-gal significantly. Possible alpha-gal sources included in the list of ingredients in zoster vaccine are porcine gelatin and bovine calf serum.<sup>1</sup> Yet neither is well documented as a source of alpha-gal. Note that although alpha-gal allergy is a potential cause of anaphylaxis following zoster vaccination, only a minority of alpha-gal–allergic patients react.<sup>7</sup> Our patient presents the enigma of a possibly tick-sensitized gelatin-allergic individual reacting to zoster vaccine while negative to alpha-gal. Although this is a single case, clinicians should be aware of the possible presence of IgE to protein epitopes on mammalian gelatin and any indicators in the patients' history that might help to predict anaphylaxis after zoster vaccine.

**TABLE I.** ImmunoCAP IgE results in sera from 4 patients with the alpha-gal syndrome and the patient with a severe reaction to Zostavax

IgE results	Subject 1	Four cases of alpha-gal syndrome			
		Subject 2	Subject 3	Subject 4	Subject 5
Total IgE	645	1180	3021	1201	838
Alpha-gal (z5)*	<0.35	<b>76.6</b>	<b>66.3</b>	<b>66.4</b>	<b>73.5</b>
Chicken (f83)	0.40	<0.35	<0.35	0.51	0.81
Turkey (f284)	<0.35	<0.35	<0.35	3.02	0.61
Beef (f27)†	0.44	18.4	26.2	16.0	12.5
Mutton (f88)†	<0.35	5.51	7.15	26.2	10.2
Cat dander (e1)†	<0.35	18.3	33.3	15.6	16.4
Pork (f26)†	<0.35	16.3	16.5	12.4	9.54
Fel d 2 (e220)	<0.35	0.49	<0.35	0.41	2.28
Gelatin (c74)	<b>5.00</b>	0.35	0.35	0.67	1.05
Bovine gelatin (z21)*	<b>26.8</b>	<0.35	<0.35	2.28	4.72
Porcine gelatin (z22)*	<b>62.9</b>	0.65	0.53	2.92	5.12
Fish gelatin (z23)*	<0.35	<0.35	<0.35	2.45	4.92

All values are in kilo units per liter (kU/L). Relevant values are shown in boldface.

All tests were run on the ImmunoCAP250 (Phadia, Kalamazoo, Mich; analytical sensitivity = 0.35 kUa/L).

\*Assays used biotinylated proteins bound to Streptavidin CAP.<sup>5</sup>

†Animals that carry alpha-gal on proteins as a major blood group substance.

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## Reply

To the Editor:

Retterer et al<sup>1</sup> note that their patient reacted to zoster vaccine, and then was primarily found to be sensitized to gelatin 3 years later, without alpha-gal-specific IgE. In their assessment, the best explanation is that the gelatin-specific IgE is more likely the culprit in the previous reaction to zoster vaccine than alpha-gal-specific IgE. They suggest for this specific patient that tick bites inoculate other antigens such as gelatin that could potentially sensitize the patient.<sup>2</sup> Alternatively, we suggest that before the availability of alpha-gal-specific IgE testing the patient may have had positive specific IgE to alpha-gal (and gelatin and beef), but the circulating alpha-gal-specific IgE antibody concentrations diminished over time, as is frequently observed in our clinics when patients successfully avoid further tick bites and red meat.<sup>3</sup>

Although the quantitative alpha-gal content of various meats clearly varies and contributes to reactions,<sup>4</sup> an important clinical observation suggested by the report of Mullins et al<sup>5</sup> is that patients who have alpha-gal allergy can often have reactions that are context specific. Some patients report reactions only to beef, whereas others react only to pork.<sup>5</sup> We have performed a 2-step challenge/administration of zoster vaccine in an alpha-gal-allergic patient avoidant of mammalian meat with declining alpha-gal-specific IgE (sIgE alpha-gal of 23.10 kU/mL, negative gelatin sIgE) and observed no symptoms, similar to what was

done by Pinson and Waibel.<sup>6</sup> In addition, we are aware of 4 more patients among our alpha-gal patients who have received zoster vaccine uneventfully despite an existing diagnosis of alpha-gal allergy demonstrated by positive sIgE to alpha-gal and appropriate clinical history. This provides additional support that not all alpha-gal-allergic patients will react to zoster vaccine.

There are a large number of clinical questions that challenge the management of alpha-gal allergy. What are the incidence and prevalence of alpha-gal in the US population? Why do some patients react to alpha-gal in one context but not another? How long does alpha-gal allergy typically last? Should patients who can tolerate alpha-gal in some contexts continue to consume it? Can we *a priori* identify individuals who are unsafe to receive certain vaccinations? We would suggest that researchers and clinicians would benefit from a multisite, collaborative, cohort study of alpha-gal allergy, with the multifold goal of determining how antigenic specificity varies between patients at the time of diagnosis and following how reactivity, specific IgE antibody concentrations, and antibody specificity change within patients naturally over time, as well as with ongoing exposure versus avoidance and with unexpected antigenic challenges.

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