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## Isolated Gastrointestinal Alpha-gal Meat Allergy Is a Cause for Gastrointestinal Distress Without Anaphylaxis

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Alpha-gal allergy is characterized by a reaction to beef, pork, and other mammalian meat and derived products, typically hours after ingestion, and is diagnosed by the presence of elevated serum alpha-gal IgE antibodies.<sup>1–3</sup> The allergy appears to develop after the bite of a hard tick and has been described in the United States (particularly the southeastern United States; Supplementary Figure 1), Europe, Africa, Australia, Central and South America, and Asia.<sup>4–6</sup> Symptoms can include pruritus, rash, diarrhea, abdominal cramping, shock, and anaphylaxis, the latter of which is defined by the involvement of 2 or more systems (skin, gastrointestinal [GI], cardiac, pulmonary). GI symptoms are caused by IgE-mediated degranulation of mast cells and histamine receptors in the GI tract.

Management of the allergy includes counseling on the avoidance of mammalian meat and sometimes dairy and other mammalian-derived products.<sup>7</sup> In case of exposure, short- and long-acting oral antihistamines such as diphenhydramine and fexofenadine may be used to ameliorate both GI and allergic symptoms.

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**Conflict of interest**

This author discloses the following: Scott P. Commins is a speaker for Genentech, receives royalties from Uptodate, and receives research grants from the National Institutes of Health and the Centers for Disease Control and Prevention. The remaining authors disclose no conflicts.

**CRedit Authorship Contributions**

Michael P. Croglia, MD (Data curation: Lead; Investigation: Lead; Writing – original draft: Equal). Scott P. Commins, MD, PhD (Conceptualization: Supporting; Writing – original draft: Supporting; Writing – review & editing: Equal). Sarah K. McGill, MD, MS (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Lead; Investigation: Lead; Writing – original draft: Equal; Writing – review & editing: Equal).

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org) and at <https://doi.org/10.1053/j.gastro.2021.01.218>.

Allergy and oncology journals have primarily published research on alpha-gal allergy, and it has not been described previously in the GI literature. We describe patients with the allergy who presented with isolated GI symptoms.

## Methods

We studied patients from 2 GI clinics in the southeastern United States who were found to have elevated serum alpha-gal IgE and GI complaints without accompanying rash, hypotension, or difficulty breathing in this retrospective cohort study. After observation by both clinic physicians that patients could have GI symptoms from the allergy, patients with functional-type symptoms were frequently screened for alpha-gal. As part of their clinical practice, patients who were alpha-gal positive were counseled to strictly avoid mammalian meat, offered a consultation with an allergist, and followed clinically. After excluding 2 patients for confounding factors (ileal Crohn's disease and daily cannabis use), we describe the remaining patients. The University of North Carolina Institutional Review Board approved the study.

Clinical endpoints were compliance with meat elimination diet and improvement in GI symptoms. We defined resolution as no symptoms on an alpha-gal-free diet, significant improvement as only occasional or mild symptoms for which patients did not seek further care, and some improvement as subjective improvement but persistent symptoms that required medical follow-up. We judged meat elimination as "strict" if patients strictly avoided mammalian meat, apart from attempts to self-challenge.

## Results

Abdominal pain (87.5%), nausea (75%), and diarrhea (68.75%), mainly episodic (68.8%) vs chronic (31.25%), were the most common symptoms among patients (Table 1). Nine patients (56.2%) met the criteria for diarrhea-predominant irritable bowel syndrome. Some patients reported awakening at night with GI distress given the typical delayed reaction. We observed variability in the response to mammalian meat in that some patients did not report a response to every exposure. No patient related GI symptoms to mammalian meat ingestion before diagnosis, and 75% recalled a tick bite. The median time from symptom onset to diagnosis was 21 months.

All patients reported symptom improvement during a median follow-up of 14 months (range, 2 months to 3 years). Four patients' symptoms resolved, all of whom followed strict avoidance diets. Eight patients (50%) reported significant improvement and 4 patients some improvement.

Six patients had moderate or severe GI distress after self-challenging with beef or pork during the follow-up period and continued on an avoidance diet (patients E, H, L, N, O, and P). Only 1 patient developed anaphylaxis at follow-up (patient E) after an attempt to self-challenge. Two patients resumed eating meat regularly during the follow-up period. Patient F had intermittent attempts to challenge after diagnosis and resumed eating meat 1 year after diagnosis, at which time she ceased to have GI symptoms. Patient K resumed eating pork but not beef soon after diagnosis and eventually returned to eating beef.

Of 16 patients, 13 (81%) followed a strict elimination diet on follow-up and 3 followed partial meat elimination. In addition, 10 patients reported eliminating dairy, 4 patients continued dairy consumption, and 2 patients did not report. Eight patients received formal diet counseling at the University of North Carolina allergy clinic. The median alpha-gal IgE was 0.61 IU/mL, much lower than the median of 51.3 IU/mL in a cohort of 24 alpha-gal-allergic patients with a history of anaphylaxis, angioedema, or urticaria.<sup>3</sup>

## Discussion

In our study, patients with alpha-gal meat allergy developed GI symptoms—most commonly episodic abdominal pain, nausea, and diarrhea—without more traditional manifestations of food allergy such as hives, angioedema, or anaphylaxis. Adhering to a mammalian meat-free diet led to significant symptom improvement or resolution in three-fourths of patients.

Within the allergy literature, reports of isolated GI alpha-gal allergy exist. Among 114 patients diagnosed with the allergy in South Africa and challenged with beef sausage under observation, 81 reacted, and among those, almost half were limited to GI symptoms—25% with vomiting and/or diarrhea and 21% with severe and persistent abdominal cramping alone.<sup>8</sup> After an observed challenge of pork sausage among 12 patients with the allergy in the United States, 2 patients developed isolated GI distress.<sup>1</sup>

This is a small observational study and has many limitations. We did not perform a formal oral challenge test, and both improvement in symptoms and reactions to meat consumption after diagnosis were based on subjective reports. There may be overlap of GI symptoms with other causes of GI distress such as lactose.

Future prospective studies would ideally involve validated patient-reported symptom measures over time. Prospective studies also could better ascertain the time frame from diet change to symptom improvement and the degree of elimination, including that of dairy, gelatin, and flavorings that contain animal-derived products, that are associated with symptom resolution.

We observed a lower median alpha-gal titer compared with other cohorts with anaphylaxis, and our patient with the highest titer did develop anaphylaxis on follow-up. However, more work is needed to define whether titer predicts severity of response. In conclusion, our findings suggest that screening with alpha-gal IgE may be a reasonable strategy in patients who live in areas with known cases of alpha-gal allergy and present with new-onset GI symptoms, particularly episodic abdominal pain, diarrhea, and nausea, even in the absence of rash or anaphylaxis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Abbreviation used in this paper:**

**GI**                      gastrointestinal

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**Table 1.**

Patient Characteristics

Patient Identification	Age Decade at Diagnosis	Sex	Months from Symptom Onset to Diagnosis; Prior GI Diagnoses	Symptoms	Alpha-gal IgE Level (IU/L)	Recalled Tick Bites	Meat Elimination	Improvement
A	50	F	2	Diarrhea, abdominal bloating, mucus in stools, fecal urgency	1.27	Yes	Strict	Resolution
B	60	F	2	Abdominal pain, nausea, heartburn	0.76	No	Strict	Resolution
C	80	M	7	Abdominal pain, diarrhea, nausea	63.6	Yes	Strict	Resolution
D	40	M	144; irritable bowel syndrome <sup>a</sup>	Abdominal pain, diarrhea, nausea, noncardiac chest pain	0.27	Yes	Strict	Some
E	60	F	36	Abdominal pain, diarrhea, nausea	>100	No	Strict	Significant
F	60	F	120	Abdominal pain, constipation, nausea, vomiting	5.24	Yes	Partial	Significant
G	80	F	60; irritable bowel syndrome <sup>a</sup>	Abdominal pain, diarrhea, nausea	0.4	Yes	Strict	Some
H	40	F	2; recurrent <i>Clostridioides difficile</i> infection <sup>b</sup>	Abdominal pain, diarrhea, nausea	0.65	Yes	Partial	Significant
I	70	F	36	Abdominal pain	0.11	Yes	Strict	Significant
J	60	F	10	Abdominal pain, diarrhea	0.53	Yes	Strict	Resolution
K	60	M	12	Abdominal pain, nausea, vomiting	0.81	Yes	Partial	Some
L	80	F	39	Nausea, vomiting	0.37	Yes	Strict	Significant
M	40	F	60	Abdominal pain, diarrhea, nausea, heartburn	0.26	No	Strict	Significant
N	60	F	10	Abdominal pain, diarrhea, nausea	0.3	Yes	Strict	Significant
O	50	F	18	Abdominal pain, diarrhea, nausea, vomiting	1.46	No	Strict	Some
P	40	M	2	Abdominal pain, diarrhea	0.57	Yes	Strict	Significant

<sup>a</sup>Patients had chronic symptoms of waxing and waning abdominal pain and diarrhea but reported moderate-to-severe exacerbations.

<sup>b</sup>The patient underwent colonoscopy-based fecal microbiota transplantation in 2018 for recurrent *Clostridioides difficile* infection that had always responded to antibiotics. Two months after the procedure, she reported awakening from sleep with severe abdominal pain and diarrhea that was *C. difficile* negative after eating a hamburger the day before.