

Table 1
Acetazolamide Oral Desensitization Protocol

Step	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Total dose (mg)
1	0.25	1	0.25	0.25
2		2	0.50	0.75
3		4	1	1.75
4		8	2	3.75
5	2.5	1	2.5	6.25
6		2	5	11.25
7		4	10	21.25
8		8	20	41.25
9	25	1	25	66.25
10		2	50	116.25
11		4	100	216.25
12		11.35	283.75	500

NOTE. Target dose 500 mg, stock concentration 25 mg/mL, and 15 minutes between doses.

Epinephrine was administered intramuscularly with nebulized albuterol and intravenous diphenhydramine. Resolution of symptoms was noted within 10 minutes of treatment.

Subsequently, skin prick (10 mg/mL) and intradermal (1 mg/mL) testing was performed with appropriate negative (saline) and positive (histamine) controls based on the report by Jachiet et al⁴ using the intravenous formulation of acetazolamide. The patient had no reaction to skin prick testing but had a 10- × 8-mm wheal reaction to intradermal testing (intradermal histamine wheal 11 × 10 mm; saline wheal negative). Similar skin testing was not performed on healthy controls. Based on the skin testing results and symptoms during the graded challenge, IgE-mediated hypersensitivity to acetazolamide was suspected and drug desensitization to 500 mg of oral acetazolamide was conducted based on the work of Castells et al¹³ (Table 1). The patient was not premedicated before the procedure and successfully completed the desensitization without symptoms. Then she was placed on 500 mg of acetazolamide 4 times daily without untoward effects, including urticaria. She has been successfully maintained on this dose for 10 months, with stabilization of vision, improvement in headaches, and decrease of CSF opening pressures.

The IgE-mediated reactions to acetazolamide have been infrequently reported and there are no prior reports in children.^{7–12} Successful desensitization to intravenous acetazolamide has been only recently reported by Gharib et al¹¹ in a 21-year-old adult patient with a history of urticaria after taking acetazolamide. The present case represents the first report of an IgE-mediated acetazolamide allergy and successful oral desensitization in a pediatric patient. Given the risk of permanent vision loss, effective and timely treatment of IIH is critically important. For patients with a history of IgE-mediated allergy to acetazolamide in whom other forms of treatment have failed, skin testing and desensitization should be considered.

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Specific-IgE to galactose-α-1,3-galactose (alpha-gal) has limited utility in diagnosing meat allergy in a tick-endemic population



Sensitization to galactose-α-1,3-galactose (alpha-gal) is considered a prerequisite to mammalian meat allergy (MMA) and can occur through tick bites, which is due to the paralysis tick, *Ixodes holocyclus*, in

Australia.¹ The onset of symptoms is typically 3 to 6 hours after ingestion of mammalian meat, but immediate reactions have been described.²

The exact nature of the antigens leading to MMA is not known, so there is no optimal testing strategy.³ Specific immunoglobulin E (sIgE) to alpha-gal is often suggested as a diagnostic in vitro test when MMA is suspected.⁴ We determined the utility of sIgE reaction

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Table 1
Association Among MMA, Tick Bite, and sIgE Reaction to Alpha-Gal

Clinical features	sIgE to alpha-gal, n (%)		P value by χ^2 test
	Positive ^a	Negative ^b	
MMA			
Yes	22 (84.6)	4 (15.4)	<.001
No	36 (39.1)	56 (60.9)	
History of tick bite			
Yes	52 (74.3)	18 (25.7)	<.001
No	6 (12.5)	42 (87.5)	
Tick bite, yes			
MMA			
Yes	22 (84.6)	4 (15.4)	.129
No	30 (68.2)	14 (31.8)	

Abbreviations: alpha-gal, galactose- α -1,3-galactose; MMA, mammalian meat allergy; sIgE, specific immunoglobulin E.

^aSpecific IgE to alpha-gal at least 0.35 kUA/L.

^bSpecific IgE to alpha-gal lower than 0.35 kUA/L.

to alpha-gal in diagnosing MMA in a tick-endemic population because it is from these regions that patients present to health care providers.

We performed retrospective analysis of results of sIgE reaction to alpha-gal in serum (ImmunoCAP, Phadia AB, Uppsala, Sweden) received by New South Wales Health Pathology at Royal North Shore Hospital (Sydney, Australia) from January 2014 through December 2016. Quantitative values were collected, and the lower limit of detection was 0.01 kUA/L. We retrieved 162 results. Thirty-two were excluded because clinical records were not available. Eleven were excluded because of duplicate assays in the same patient. Clinical history was collected, including demographics, presence or absence of MMA, and history of tick bite and atopy (history of asthma, rhinoconjunctivitis, or eczema or documented sensitization to allergens by skin prick testing or sIgE).⁵ A patient was classified as having MMA if there was a clinical presentation of urticaria, angioedema, gastrointestinal symptoms, and anaphylaxis, alone or combined, 3 to 6 hours after ingestion of meat or an immediate reaction within 1 hour of ingesting mammalian meat innards and response to mammalian meat restriction,⁶ with other causes of the reaction excluded by investigations such as skin tests, laboratory assays, and endoscopy.

We used the χ^2 test for the association between dichotomous variables. Fisher exact test was used when expected cell counts were small. Receiver operating characteristic curve analysis was performed to evaluate the discriminatory ability of sIgE reaction to alpha-gal for a diagnosis of MMA. To control for the major confounding factor of history of tick bite, analysis was performed within a subgroup in which all patients had a history of tick bite.

A total of 118 results were included. Patient age ranged from 7 to 83 years. We used a cutoff for positivity of 0.35 kUA/L.²

Twenty-six patients had a diagnosis of MMA. Twenty-two (84.6%) had a positive sIgE reaction to alpha-gal. Although a strong association was observed between MMA and sIgE reaction to alpha-gal higher than 0.35 kUA/L ($P < .001$), 36 of 92 patients without MMA (39.1%) also had an increased sIgE level to alpha-gal.

There was a strong association with tick bite, with 52 of 70 patients having sIgE reaction to alpha-gal higher than 0.35 kUA/L (74.3%; $P < .001$). Forty-eight had no history of tick bite, of which only 6 (12.5%) had an increased sIgE reaction to alpha-gal. Stratifying by history of tick bite, there was no association between MMA and sIgE reaction to alpha-gal ($P = .13$; Table 1).

Receiver operating characteristic curve analysis showed sIgE reaction to alpha-gal was an excellent indicator of a history of tick bite (area under the curve [AUC] 0.86, 95% confidence interval [CI] 0.79–0.93) at an optimal cutoff of 0.175 kUA/L and a good indicator for MMA (AUC 0.81, 95% CI 0.73–0.90) at an optimal cutoff of 0.135 kUA/L. Of patients with a history of tick bite, the performance of sIgE reaction to alpha-gal to diagnose MMA was relatively poor

(AUC 0.67, 95% CI 0.54–0.80) even at the optimal cutoff of 16.5kUA/L. Using the currently accepted cutoff of 0.35 kUA/L, sensitivity was 85%, but specificity poor at 32%, with 30 false positives for MMA. Hence, sIgE reaction to alpha-gal was of limited diagnostic utility for MMA in a tick-endemic population, because the performance of the test to classify diseased vs non-diseased subjects after a tick bite was poor across the range of cutoffs. No significant association with atopy ($P = .64$) was identified.

Our cohort is derived from patients who reside in a tick-endemic area and seek referral for evaluation of symptoms that could be consistent with MMA and not representative of the general population. Specific IgE reaction to alpha-gal was ordered in that clinical context. We contend this makes our data more useful because sIgE reaction to alpha-gal should not be used as a general screening tool. This pertains to food allergy in general.

In our patient cohort, sIgE reaction to alpha-gal did not add value as a diagnostic test. After stratifying by history of tick bite, there was no association between sIgE reaction to alpha-gal and MMA ($P = 0.13$). Its performance in identifying subjects with MMA was poor (AUC 0.67).

Before this study, it had been reported that sIgE reaction to alpha-gal can increase 20-fold after tick bite from *Amblyomma americanum* and be sustained despite the absence of MMA.⁷ In Tramonti, Italy, tick bite history was found to be correlated to positive sIgE reaction to alpha-gal.⁸ In 300 forest workers exposed to *Dermacentor reticulatus* and *Ixodes ricinus* in southwest Germany, the prevalence of sIgE reaction to alpha-gal of at least 0.10 kUA/L was 35.0% and that for a reaction of at least 0.35 kUA/L was 19.3%.⁹ MMA was present in only 8.6% with sIgE reaction to alpha-gal of at least 0.35 kUA/L.⁹

Other confounding variables include administration of cetuximab and gelofusine,⁴ atopy,^{8,10} cat dander sensitization,¹⁰ and helminthic infections or schistosomiasis. There was no significant association of positive atopy status to positive sIgE reaction to alpha-gal in our cohort.

There are limitations to our study. Diagnosing MMA is difficult. Oral food challenges were performed in a minority of patients. Skin tests using commercial or fresh extracts are not highly sensitive and do not perform consistently.¹

We did not perform a comparison study examining the prevalence of sIgE reaction to alpha-gal and MMA in a non-tick-endemic cohort in Sydney, Australia, because this was not an epidemiologic study. Such a study would determine the utility of sIgE reaction to alpha-gal in the nonendemic population for MMA.

In summary, sIgE reaction to alpha-gal is strongly associated with patient history of tick bite in our tick-endemic population, rather than a diagnosis of MMA, and this can be ascertained in most cases at clinical review.

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