

Clinical Management Review

Diagnosis and Management of Patients with the α -Gal Syndrome

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The galactose- α -1,3-galactose (α -Gal) syndrome has many novel features that are relevant to diagnosis and management. In most cases, the diagnosis can be made on a history of delayed allergic reactions to mammalian meat and the blood test for IgE to the oligosaccharide α -Gal. In general, the diagnosis also dictates the primary treatment, that is, avoiding mammalian meat and also dairy in some cases. In the United States, the lone star tick is the primary cause of this disease, but different ticks are responsible in other countries. Blood levels of IgE to α -Gal often drop in patients who avoid recurrent tick bites, but the rate of decline is variable. Similarly, the delay before reactions is variable and the severity of the allergic reactions is not predicted by the delay or the titer of specific IgE. Some mammalian-derived products such as heart valves, gelatin-based plasma expanders, and pancreatic enzymes are relevant to only select patient groups. A minority of cases may benefit from avoiding a wide range of products that are prepared with mammalian-derived constituents, such as gelatin. This review focuses on the nature of the syndrome, common challenges in diagnosis and management, and also gaps in our current knowledge that would benefit from additional investigation. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: α -Gal; Anaphylaxis; IgE to oligosaccharide; Glycolipids; Red meat allergy

INTRODUCTION

In 2006 the mAb cetuximab was approved for the treatment of cancer of both head and neck and the colon.¹ It soon became clear that allergic reactions were occurring in major clinics in the southeast of the United States.² Significantly, Dr Tina Merritt obtained serum from 2 severe cases that occurred in Fayetteville,

Arkansas, and in addition we had developed the technique of measuring specific IgE (sIgE) using biotinylated proteins on a streptavidin ImmunoCAP.³ In collaboration with both Bristol-Myers Squibb and ImClone we received pretreatment sera from 76 patients who had received cetuximab, of which 41 came from Bristol-Myers Squibb and 35 came from Dr Christine Chung and her colleagues⁴ in the medical oncology group at Vanderbilt. Those studies demonstrated that the patients who had reactions had preexisting IgE specific for cetuximab and that the target of those antibodies was the oligosaccharide galactose- α -1, 3-galactose (α -Gal) on the antigen-binding fragment (Fab) portion of the mAb.^{4,5}

Before 2006 we had seen at least 5 patients in the clinic who reported adult onset of allergic reactions related to eating meat. Those subjects described surprisingly long delays between eating meat and the reactions, and prick test wheal diameters to beef and pork were very small, that is, 3 mm or less. Thus, like most other allergists, we could not make sense of their histories. During 2007 we looked in our allergy clinic for patients who had IgE specific to α -Gal comparable to that found in cancer patients who had reactions to cetuximab. Those studies identified that it was the patients who reported delayed reactions to mammalian meat (often called red meat) who had IgE specific for α -Gal. Furthermore, when we presented the early results to a meeting in Kansas City, Missouri, Dr Barrett D. Lewis came forward and said, "I have similar cases in Springfield, MO." He sent us sera on 12 cases, 11 of whom had IgE specific to α -Gal and were included in the original article describing the syndrome.⁶

During 2007 it became clear that cases of delayed anaphylaxis to red meat were present in the same area as reactions to cetuximab. Internet search suggested that this area, that is, Virginia, North Carolina, Tennessee, Arkansas, southern Missouri, and eastern Oklahoma, was similar to the maximum area of Rocky Mountain spotted fever reported by the Centers for Disease Control and Prevention.⁷ Accepting this association and the implication that this form of sensitization might relate to tick bites we questioned dozens of patients about the number of tick bites they had received. Those results supported a strong association between bites from the lone star tick, *Amblyomma americanum*, and the syndrome.⁸ In addition, a history of prolonged itching at the site of tick bites was a significant predictor of sensitization.⁸ Finally, we followed rises in sIgE after tick bites in 3 cases, 2 of whom developed delayed urticarial reactions to red meat.⁸ Strikingly, none of the patients reported a severe febrile illness comparable to clinical Rocky Mountain spotted fever, which is actually rare in this area.^{7,9} It is now clear that it is unusual for *A. americanum* ticks to carry *Rickettsia rickettsii*, but in contrast most lone star ticks in this area carry the related *R. amblyommatis*.⁹ Thus, it appears

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Abbreviations used α -Gal- Galactose- α -1,3-galactose

Fab- Antigen-binding fragment

sIgE- Specific IgE

that the febrile illnesses with positive Rickettsial serology that are sometimes classified as Rocky Mountain spotted fever are likely to be caused by *R amblyommatis*, or other spotted fever group Rickettsia, which can cause positive Rickettsial serology but only mild symptoms.^{10,11} The details that explain the connection between tick bites and α -Gal sensitization remain an open question, but it is increasingly clear that certain ticks can express α -Gal and that tick antigens can have potent IgE-inducing properties.¹²⁻¹⁵ The known properties of α -Gal as a blood-group-like antigen of nonprimate mammals fit with the reported specificity of the allergic reactions to red meat from mammals that carry α -Gal.¹⁶

At the American Academy of Allergy, Asthma & Immunology meeting in 2008 we presented the story about α -Gal and learned about earlier reports suggesting a connection between tick bites and the onset of allergy to meat. In 2006, Van Nunen et al¹⁷ reported meat allergy cases related to tick bites in Sydney, Australia, which she published in 2009. Dr Deutsch in Athens, Georgia, had reported 5 very similar cases to the Georgia Allergy Society in 1989.¹⁸ The importance of these cases is that they clearly show that the syndrome had been in existence before we became aware of it. Dr Marianne van Hage and her colleagues¹⁹ had also identified that sera from some cat-allergic patients had IgE specific for an oligosaccharide on cat IgA. That epitope was later shown to be α -Gal, and the group in Sweden has now established the relevance of bites from the tick *Ixodes ricinus* to α -Gal sensitization and red meat allergy in southern Sweden.²⁰⁻²²

THE CLINICAL SYNDROME AND DIAGNOSIS

Today we have extensive experience with classical cases of the α -Gal syndrome (Table 1, A).

1. They have onset in adult life after eating meat without problems for many years.
2. Reactions range from localized hives or angioedema to severe anaphylaxis, which requires emergency treatment and admission to hospital.
3. Reactions start 2 to 6 hours after subjects have eaten meat of mammalian origin, and the severity of reactions is not predicted by the delay.^{23,24}
4. They have positive sIgE for α -Gal. If the antibodies are greater than or equal to 2 IU/mL or more than 2% of the total IgE, this makes the diagnosis very likely. We often measure total IgE because some cases are nonatopic and have low total IgE.²⁴ Recently, we saw a case with a convincing history whose total serum IgE was 6.0 IU/mL and sIgE to α -Gal was 0.8 IU/mL. Thus, although the sIgE was less than 1.0 IU/mL, it was nonetheless more than 10% of the total IgE.
5. The final element of diagnosis depends on how they respond clinically to a diet avoiding red meat.²⁵ From conversations with allergists working in areas with a large number of cases it appears that at least 80% of cases fit the classical description, where both diagnosis and primary treatment are relatively straightforward.

However, it is important to realize that many cases do not present classically. For example, there are a significant number of pediatric cases and the published data suggest that the condition in children has similar features.²⁶ In particular, the specificity and titer of sIgE, the delay between eating meat and reactions, the relationship to tick bites, and the response to diet are all similar.^{24,27,28} Another exception to the rule relates to the delay in symptom onset. Most evidence is consistent with a delay of 2 to 6 hours; however, a recent study found that 16% of subjects with the syndrome reported subjective symptom onset in less than 2 hours.²⁴ Moreover, faster reactions were reported in a recent cohort from South Africa,²⁸ and have been consistently observed with pork kidney, both in clinical practice and in challenge tests.²⁹⁻³¹

In terms of diagnosis it became clear in early studies that prick tests with extracts of beef or pork were unreliable.⁶ Sensitization can be investigated using intradermal skin tests to beef, pork, and milk as well as chicken, turkey, and fish as negative controls.⁶ However, few clinics carry out intradermal tests for food antigens and most allergists rely on a blood test for IgE to α -Gal. There are no strict criteria for what sIgE levels equate with the diagnosis, though the preponderance of our patients have IgE specific for α -Gal that is at least 1% of the total IgE. Diagnostically there are 2 groups that often cause confusion: first, patients with an unclear history who are found to have IgE to α -Gal and second, patients who give a history of reacting to mammalian products but whose blood test result is negative for IgE to α -Gal.

What is the range of symptoms that can occur in relation to the syndrome?

In our practice the most important group of nonclassical symptoms is those that involve the gastrointestinal tract. Gastrointestinal elements are not uncommon as part of reactions that include hives. However, there are patients who have episodes of abdominal pain without any skin involvement. Those cases are a problem because the possibility of food allergy is not obvious, and they can be severe. Indeed, 2 of the most severe cases we are aware of manifested with significant gastrointestinal symptoms but little if any dermatologic involvement. Interestingly, there have been very few subjects who have reported itching in the mouth or swelling of the oral tissue. Other diagnoses that arise less commonly are arthritis and chronic pruritus.²⁴ Distinguishing α -Gal from chronic hives can be challenging, and there are some cases where the 2 entities may overlap.³² In any case where the history is atypical but the sIgE is positive, the question that should be asked is whether they improve with avoidance of red meat or full avoidance of mammalian products. It is important to remember that random cohorts of subjects in Tennessee, Virginia, and North Carolina have found that 15% or more of the population has IgE to α -Gal.^{4,27,33} Thus, there must be many subjects who do not experience allergic symptoms despite having the sensitization.

Seronegative subjects with allergic responses to 1 or more mammalian products

Obviously there are plenty of children with traditional immediate allergy to mammalian foods, but these are primarily related to proteins also present in cow's milk and have typical rapid onset.³⁴ The cases we are interested in here are those with onset later in childhood or as adults who do not always react

TABLE I. Clinical cases that reflect examples of allergic reactions to mammalian antigens in adults**A. Severe anaphylactic cases in patients with specific IgE to α -Gal**

Case 1: Anaphylaxis to "the other white meat"	Female employee of the medical center, age 79 y. Mild episodes were suspicious for the syndrome; however, she thought pork was a "white meat." She ate pork for lunch, started itching 3 hours later, and soon thereafter collapsed in the lobby. She required resuscitation with intravenous fluids, Solu-MEDROL, and repeated adrenaline and was admitted overnight. Her α -Gal sIgE was 82.7 IU/mL and tryptase was 36.5 ng/mL.
Case 2: Abdominal pain	A 45-year-old woman had multiple episodes occurring many hours after eating: full GI workup including esophagogastroduodenoscopy and colonoscopy did not reveal a cause. History of multiple tick bites including "chiggers." Several episodes started with abdominal pain and diarrhea. She was found collapsed on the bathroom floor mentally confused and was admitted to hospital overnight. Her IgE to α -Gal was 69.7 IU/mL, and she had a good response to a diet including dairy avoidance.
Case 3: Anaphylaxis with transient loss of sight	A 63-year-old policeman living in rural Virginia experienced 3 tick bites and after that he had 3 mild episodes of hives. Three hours after eating "London broil" he developed itchy hives and "had to sit down." Found to have blood pressure of 40/0 and reported to EMS "I can't see." Required full resuscitation in the emergency department including adrenaline drip overnight. Sight returned after 3 h. His IgE to α -Gal was 23 IU/mL, tryptase was 95.5 ng/mL, and he had a full recovery on an avoidance diet.

B. Allergic reactions to other mammalian products "masquerading" as α -Gal

Case 4: Pork-cat syndrome	A 19-y-old woman with chronic GI symptoms associated with eating meat. Known tick exposure and also allergic to cat. IgE to α -Gal was 0.13 IU/mL, total IgE of 1406 kU/L, cat dander >100 IU/mL, IgE to cat serum albumin 29.5 IU/mL, pork serum albumin 18.6 IU/mL. She responded to a diet avoiding pork.
Case 5: Anaphylaxis to vaccine containing gelatin	Patient with reactions to barbecue and other meat for several years who experienced a severe reaction within 20 min of shingles vaccination (Zostavax). She collapsed and required full resuscitation and hospitalization. Her IgE to α -Gal was negative, but her IgE to gelatin was 5 IU/mL. Additional assays prepared in our laboratory showed IgE to bovine gelatin of 26.8 IU/mL and pork gelatin of 62.9 IU/mL.
Case 6: Recurrent allergic reaction to milk and red meat	Woman aged 66 y with history of "insect" bite reported periodic facial itch and swelling at night. Initially regarded as mammalian meat allergy, with IgE to α -Gal level of 0.11 IU/mL. Her episodes continued despite avoiding meat, including more severe swelling of face and throat. Found to have IgE to cow's milk 72.9 IU/mL and IgE to BSA (Bos d 6) of >100 IU/mL and responded to dairy-free diet.

GI, Gastrointestinal.

rapidly and have symptoms related to mammalian proteins (see Table I, B). The first group that became clear was the pork-cat syndrome. Although pork-cat was long recognized in Europe it had been ignored in the United States.^{35,36} Most of the early cases we saw had been referred as possible cases of α -Gal syndrome³⁷ and in a recent investigation of 261 subjects reporting red meat allergy, nearly 2% had an IgE signature suggestive of pork-cat (ie, positive sIgE to cat, serum albumin of cat [Fel d 2], and serum albumin of swine [Sus s 1]).²⁴ At present, there is no clear explanation for why they present as adults. We have not carried out challenges on pork-cat syndrome, and it is our judgment that none of the 3 cases reported in Table I, B, would have agreed to a challenge. However, there are occasional cases where a challenge may be necessary to resolve confusion.

MANAGEMENT**The natural history of the syndrome and relevance of tick avoidance**

Following patients in the clinic, including questions about symptoms, diet, and further tick bites, some aspects of natural history are already clear. First, all patients should be informed that further tick bites can maintain or lead to increases in the titer of IgE to α -Gal.^{38,39} In contrast, most subjects who successfully avoid tick bites will experience a decrease in their α -Gal sIgE.³⁹ Although the rate of decline is variable and it is not clear what degree of decrease is required to successfully regain tolerance, we have followed many patients whose titers became negative (ie, <0.1 IU/mL) and who re-introduced meat in their diet on their own. Avoiding tick bites in rural or suburban areas is

difficult, but normal avoidance measures, that is, appropriate clothing and sprays, can be effective.⁴⁰⁻⁴² The strongest evidence for sensitization to α -Gal relates to ticks, but it is possible that other ecto-parasites such as "chiggers" could also be relevant.⁴³ A complex question is why some people who live and work in an area with ticks do not become sensitized. This question may have 2 elements: first, are all individuals equally "attractive" to ticks? Multiple anecdotal stories report that ticks favor some subjects. Second, there are patients who report tick bites that do not itch and they do not usually become sensitized. There is currently no solid information about the characteristics that predict either the tendency to get tick bites or the likelihood of becoming sensitized after being bitten. It is clear, however, that many subjects who are not traditionally atopic (ie, do not produce IgE to aeroallergens) can nonetheless develop sensitization to α -Gal and acquire the syndrome after getting tick bites. Levels of α -Gal sIgE and also the clinical presentation are similar in nonatopic subjects and their atopic counterparts.²⁴

A question that often arises is whether eating red meat is alone sufficient to induce an IgE response to α -Gal. Our own published data provide strong evidence that people living in an area without ticks, such as Northern Sweden or New York City, do not develop sensitization to α -Gal or the syndrome despite eating large quantities of beef or pork.^{8,33} The same data also argue against a role for other mammalian exposures, such as cat ownership, in developing IgE to α -Gal. We are unaware of any data that have looked at whether eating red meat can influence the levels of α -Gal sIgE in subjects who have the syndrome. An additional point is that some subjects with the syndrome may tolerate red meat on some occasions with few or no symptoms

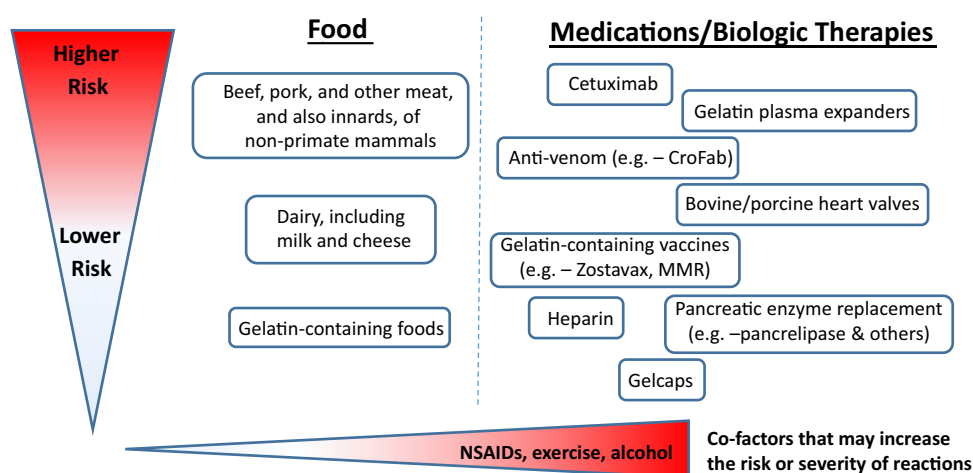
Risk of reactions in the α -Gal syndrome

FIGURE 1. The risk and also severity of reactions in the α -Gal syndrome relate to the amount of the oligosaccharide that is present in food, drugs, or other therapeutics. The route of administration is relevant to the speed at which reactions occur; that is, intravenous administration is associated with rapid reactions, whereas oral ingestion has delayed onset. Cofactors such as NSAIDs, exercise, and alcohol can be additional risk modifiers. This schematic reflects clinical experience, as well as challenge studies and laboratory investigations. *CroFab*, Crotalidae polyvalent immune Fab; *MMR*, measles, mumps, and rubella; *NSAID*, Nonsteroidal anti-inflammatory drug.

but have severe reactions on others. This intraindividual variability is often not explained by the amount of meat and may reflect differences in the quantity or form of α -Gal that is present in the meat or could reflect the importance of cofactors such as exercise, nonsteroidal anti-inflammatory medications, and alcohol in modifying the allergic response.⁴⁴ In regard to the natural history of subjects who are sensitized but asymptomatic, there are currently no population-based follow-up studies and we are not in a position to recommend management of these cases except to avoid tick bites.

Avoidance of “red” meat

The primary advice for newly diagnosed cases of the syndrome is to completely avoid meat of mammals (Figure 1). In most areas of the United States, this means beef, pork, and lamb.⁶ However, internal organs are equally or more able to induce reactions.⁴⁴ This includes kidneys, liver, heart, and intestines (tripe), but the evidence is strongest for pork kidneys.^{29,31} In Europe and most other countries, many other animals are eaten, including rabbit, horse, goat, and so forth.²⁹ In rural United States, it is worth mentioning that venison and bear meat and also many other small animals that can become part of “Brunswick stew” are all mammals.

The case for avoiding dairy products

We do not include avoidance of dairy products as part of primary avoidance, because most of the patients do not react to milk or cheese (Figure 1). This is not because glycoproteins or glycolipids carrying α -Gal are absent from dairy products. Indeed it has been clear since 2009 that these patients have IgE antibodies that recognize α -Gal in cow’s milk extract, and give positive skin reactions to milk.⁶ Until recently the primary reason for recommending full avoidance of dairy products has been inadequate control of symptoms in subjects avoiding red meat.

Many of those patients have subsequently responded to a diet that also includes dairy avoidance. Avoiding products such as milk, yogurt, and ice cream is relatively easy because there are alternatives made from almond, oat, cashew, or other non-mammalian sources. The thing that patients miss most is English or French cheeses.⁴⁵

The argument about a dairy-free diet changes completely if consumption of α -Gal-containing products can contribute to inflammation without giving rise to allergic symptoms. Before the recognition of IgE to α -Gal, the cardiovascular group in Cambridge reported that patients with triple vessel coronary artery disease had a distinct pattern of IgG and IgD specific for α -Gal.⁴⁶ In 2018, we reported that there was significantly worse coronary artery disease in patients who had IgE to α -Gal.⁴⁷ That study needs confirmation, but it implies that the risk related to IgE to α -Gal is not restricted to subjects who have allergic reactions. If it is true that patients with IgE to α -Gal have an increased risk of atherosclerosis even if they do not have allergic symptoms there are 2 groups of subjects who may need to be advised to go dairy free as well as avoid red meat: First, patients whose symptoms are “controlled” by avoiding red meat and second, subjects who have IgE to α -Gal but have not recognized symptoms related to red meat. The evidence at present is not strong enough to make this as a recommendation, but clearly it is an area that needs more research.

Additional considerations for managing the syndrome

There are “hundreds” of ways in which food and other products that are not obviously mammalian could nonetheless have products from mammals added during preparation or manufacture.⁴⁸ The evidence for the presence of α -Gal in these different food and medical products varies markedly, with some items clearly expressing the oligosaccharide (eg, cetuximab) and

TABLE II. Categorization of food and medical products that are or may be problems in subjects with the α -Gal syndrome, stratified by relative risk

Management/risk category	Type	Source	Reference
Primary	Foods	• Red meat (beef, pork, lamb, deer)	6,23
		• Innards (pork kidney, liver, heart, intestines)	29,31
		• Pork gut casings for sausages	
	Medicines	• Cetuximab	4
		• Gelatin-based colloid plasma substitute (Gelafundin)	49,50
Secondary	Foods	• Dairy (milk, cheese, yogurt, butter)	49
		• Gelatin (marshmallows, jelly babies, other sweets)	49,51
		• Collagen (eg, beef collagen casings)	52
		• Lard	
	Medicines	• Gelatin-containing vaccines (Zostavax, MMR, yellow fever)	53-55
		• Bovine and porcine heart valves	56,57
		• Pancreatic enzyme replacement	58
		• Crotalidae polyvalent immune Fab	59,60
Incomplete data	Foods	• Canned tuna (contaminated with dolphin or whale)	
		• Chicken or fish cooked on a contaminated grill	
	Medicines	• Gelatin: eg, gel caps, Floseal hemostatic matrix, Surgifoam powder, absorbable gelatin sponge, gabapentin oral solution, lidocaine patch*	61-63
		• Heparin†	64
		• Stearic acid and/or magnesium stearate: eg, many tablets, including acetaminophen, oxycodone, lisinopril, oxycontin†	61
		• Glycerin, eg, many suspensions, including acetaminophen liquid, methadone solution, ibuprofen suspension†	61
		• Lactose and derivatives, eg, aspirin, haloperidol injection, and hydromorphone injection†	61

MMR, Measles, mumps, and rubella.

Risk/management categories: Primary: Considered high risk and avoidance recommended for all subjects with the active syndrome. Secondary: Some subjects can tolerate without allergic reactions but should be used with caution (there is clear evidence these products can contain α -Gal). Incomplete data: See footnotes below.

*Insufficient data: Limited evidence or case reports suggesting these products may contain α -Gal and contribute to clinical reactions in some patients with the syndrome.

†Insufficient data: Although heparin, stearic acid, glycerin, and lactic acid are or can be derived from mammals, there is no evidence that these products intrinsically have α -Gal epitopes. It is possible that α -Gal is present as a “contaminant”; however, there is little evidence that this would be sufficient to contribute to symptoms.

other products being labeled by some groups as “risky” seemingly only because there is some constituent that is derived from mammals (eg, magnesium stearate and glycerin). Although in many cases the data are insufficient to make informed judgments, we think it is worthwhile to attempt to create a framework for thinking about relative risk and by extension management of the syndrome (Figure 1 and Table II).

a. Nonmeat, nondairy food products

- i. *Pork gut casings for sausages*: Many varieties of sausages use casings derived from pork gut. Hence, chicken and turkey sausages, which would otherwise be safe, can induce anaphylactic or other reactions. We have seen at least 5 patients who reacted clinically after eating chicken or turkey sausage that had a casing made of pork gut. Today most sausages are labeled correctly but caution is necessary.
- ii. *Mammalian fat in foods*: Lard (rendered pork fat) is an important element of cooking, not only in pastry. Fat may also be added to mashed potatoes to add flavor, and pork fat is often added to venison either to add flavor or to make venison burgers. Thus, hunters who can normally tolerate venison may react if it has had pork fat added. Suet (unrendered fat from sheep or cattle) is also used in cooking, for instance, as part of mince meat.
- iii. *Gelatin*: Gelatin is a glycoprotein that is normally derived from collagen in the skin or hooves of cows or other large

mammals. This protein can carry α -Gal epitopes but the quantity of the oligosaccharide varies according to the methods of extraction. In regard to food, gelatin is a main ingredient of jelly babies, marshmallows, and jello. We have seen cases of severe reactions in people after eating marshmallows and a detailed report that included challenge tests has confirmed reactions to jelly babies.⁵¹

- iv. *Tuna and dolphins*: We have heard reports of apparent reactions to canned tuna where the possible explanation is contamination of the tuna with dolphin, which is mammalian. This is a good example of a situation where it would be helpful to have an assay for α -Gal in foodstuff.

b. Other medical uses of mammalian proteins or parts

- i. *Monoclonal antibodies*: Despite the fact that many mAbs that are in clinical use are generated in nonprimate mammalian cell systems, the evidence for α -Gal expression on most monoclonals other than cetuximab is minimal.⁵ One exception is infliximab, which has been shown to express low amounts of the glycan and has been linked to reactions in a small number of subjects with the α -Gal syndrome.⁶⁵ The reason why α -Gal glycosylation of the Fab occurs selectively on cetuximab as compared with other monoclonal is likely due to differences in the cell lines used in production. Cetuximab is produced in mouse SP2/0 cells, whereas most other monoclonals are generated in other cell lines, such as Chinese hamster ovary cells. The specific amino acid sequence in the Fab

of cetuximab could also play a role in favoring glycosylation.

ii. *Gelatin-containing medications:*

1. Gelatin is present in some vaccines, including Zostavax and measles, mumps, and rubella vaccine. Cases of reactions to these vaccines in patients with IgE to α -Gal have been reported.^{53,54} However, reactions to vaccines have also occurred in patients who had IgE to gelatin, but not to α -Gal⁵⁵ (Table I, B).
2. Gelatin is used as a plasma expander in some countries, particularly Australia and the United Kingdom.^{49,66} Gelafundin is one such plasma expander; in fact, it has been used by some groups when skin testing for α -Gal.⁶⁷
3. Gelatin-based capsules are used for many medicines and may give rise to symptoms in a small proportion of patients. Certainly they can add confusion in cases where a mammal-free diet has not successfully controlled symptoms (see Table II).

iii. *Enzyme replacement:* The pancreatic enzymes that are used for replacement in some cases of cystic fibrosis or other causes of pancreatic failure are purified from the pancreas of large mammals. These proteins, and also other mammalian-derived enzymes, have been shown to express α -Gal and have functional activity in basophil activation tests.⁵⁸

iv. *Bovine or porcine heart valves:* Soon after the description of α -Gal we heard reports of patients who experienced hives or even a mild episode of anaphylaxis after transplantation of mammalian heart valves.⁵⁷ We then became aware that Dr Ankersmit and colleagues⁶⁸ in Vienna, Austria, had reported that transplantation of mammalian valves could cause an increase in IgG to α -Gal. Recently, there have been reports that mammalian valves degenerate more rapidly in patients with IgE to α -Gal.⁵⁶ This is a problem that should be solved by using α -Gal knockout pigs as a source of heart valves.^{69,70}

v. *Antivenom:* The presence of α -Gal epitopes in antivenom formulations, which are purified Fabs derived from polyclonal IgG of venom-immunized nonprimate mammals, was convincingly shown by Fischer et al.⁵⁹ Importantly, the antivenom elicited basophil activation in an *in vitro* experiment with cells derived from a subject with the α -Gal syndrome. There has been at least 1 case report of an acute reaction to Crotalidae polyvalent immune Fab in an α -Gal-sensitized subject that was attributed to the α -Gal syndrome.⁶⁰

vi. *Heparin:* It is not obvious that the polysaccharide heparin, which itself does not appear to carry α -Gal, should be a problem in patients with the α -Gal syndrome. Nonetheless, there have been a small number of case reports that have raised the possibility and we are currently consulted on this question with some frequency.^{64,71} Heparin is a glycosaminoglycan derived from pig intestine, and it is possible that some batches could be contaminated with glycosylated molecules derived from the pig. Alternatively, it is possible that the IgE response to tick bites in some patients includes a wider range of specificities.⁷² The fact that cases have only rarely been reported in the University of North Carolina, the University of Virginia, or Vanderbilt suggests that

IgE-related reactions to heparin are uncommon, but this topic warrants additional investigation.

vii. *Magnesium stearate, and so forth:* There have been rare reports of subjects with α -Gal syndrome who experienced reactions that were attributed to oral medications, even those that did not contain gelatin. Magnesium stearate, which can be sourced from mammalian fat (ie, stearic acid), was described as a likely culprit in one such case.⁶¹ Given that magnesium stearate is not structurally similar to α -Gal, the implication was that residual α -Gal could be present as a contaminant in some preparations.

Alternative medical approaches

We are aware that there are some alternative/complementary medical approaches being offered in the community for the treatment of the α -Gal syndrome, for example, auricular acupuncture and kinesiology. An interesting possibility is that the apparent efficacy observed in some of these cases actually reflects the natural history of the syndrome; that is, α -Gal sIgE levels can drop rapidly in some cases.

AREAS OF ONGOING RESEARCH

Why do ticks give rise to the IgE response to α -Gal?

Before the evidence focused on ticks, many other possible causes of this form of sensitization were considered including local plants or fungi and even nematode worms. However, the experience in Virginia suggested that sensitization was primarily, if not exclusively, caused by bites of the lone star tick. Although the lone star is restricted to North America, sensitization to α -Gal in other countries has also been associated with the bites of different species of ticks (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Certainly, *A. americanum*, *Ixodes ricinus*, and *I. holocyclus* are each the most common cause of bites in the United States, Sweden, and Australia respectively.^{8,22,73} Several groups have now carried out investigations on ticks.^{12,13,21,74} None of those studies suggest that the production of α -Gal is a special property of the lone star tick. At present it seems likely that several species of ticks express α -Gal and have salivary constituents that can promote T_H2-related immunity. In keeping with the general tick theory there is some evidence that other ticks in the United States can cause sensitization. In an area of northern Wisconsin and northern Minnesota where *A. americanum* is not established, typical cases of the syndrome have been anecdotally related to bites of "wood ticks," that is, *Dermacentor variabilis*.

Mouse and other animal models of the IgE response to tick bites

There is good evidence that either bites of live ticks or intradermal injections of tick extract will induce an increase in serum IgE in mice.^{15,74} However, "wild-type" mice express α -Gal on proteins and lipids and do not make IgE to α -Gal. To solve this problem, strains of mice with the gene for α -1,3-galactosyltransferase knocked out (α -Gal knock-out mice) are used to study IgE production.^{15,74,75} There are many questions that remain to be answered about IgE responses to oligosaccharides in humans; however, there is already significant data about the role of T cells in mice. A recent article clearly demonstrates the relevance of T cells for the IgE response to tick extracts.¹⁵ Interestingly, in earlier studies on the basis of production of IgG and IgM specific for α -Gal by human B cells, the

evidence strongly implicated natural killer T cells as the source of T-cell help.⁷⁶ The importance of this is that natural killer T cells can be activated by glycolipids.

What is the mechanism of the delay before onset of symptoms and can this mechanism also be relevant to understanding chronic inflammatory effects of α -Gal exposure?

The delay between eating red meat and the onset of symptoms has 2 elements: first, the patients deny any early symptoms (either oral or systemic), and second, that despite delays of 2 to 6 hours, symptoms can come on rapidly and episodes can be severe (Table 1). Because *in vitro* activation of basophils will occur within 20 minutes of exposure to α -Gal and intradermal skin tests to cetuximab or beef develop within 15 minutes, it seems likely that the delay in symptoms reflects delayed arrival of the relevant form of antigen to mast cells that reside in peripheral tissues. Two things lead us to think about lipids; first, many hunters said that venison was less of a problem than meat from domestic mammals. Venison meat comes from true wild animals and has very little fat. Indeed, making “venison burgers” requires addition of fat to make it stick together. Second, patients reported reacting after eating fat or pastry made with lard. The importance of this “glycolipid hypothesis” comes because it links together the relevance of fat, the delay in symptoms, and the possible relevance to inflammation in arteries.^{47,77,78} In normal digestion, fat is assembled into chylomicrons, which enter the circulation after 2 hours. Over the next few hours, the fat is converted into low-density lipoprotein and high-density lipoprotein, which involves a change in particle size from 300 nm down to 20 or 10 nm. The important fact for the argument is that low-density lipoprotein or high-density lipoprotein can pass through the endothelial wall without inflammation. The hypothesis has to be that these particles derived from mammalian meat or fat can activate mast cells either in the skin or in arterial walls.^{78,79} This idea is supported by the recent report of Roman-Carrasco et al⁸⁰ who demonstrated that α -Gal carrying glycolipids from beef, but not glycoproteins from beef, could transit through a Caco-2 epithelial barrier model and be packaged into chylomicrons.

CONCLUSIONS

In the 10 years since the first description of delayed allergic reactions to mammalian meat, the α -Gal syndrome has become well recognized in many continents including Australia, Europe/Asia, and North America. The features that distinguish this syndrome from other forms of food allergy include (1) onset as an adult or late in childhood, (2) a relationship to previous tick bite(s), (3) the fact that the epitope for the IgE response is an oligosaccharide, and (4) the characteristic delay between eating mammalian meat and onset of the symptoms. Many issues have arisen about the range of symptoms that develop in patients who are sensitized to α -Gal, but in most cases (~80%) management by avoidance of red meat (and organs) is sufficient. A minority of cases (~5%-20%) also need to avoid dairy and gelatin. A small minority of cases (~≤1%) needs to be aware of the large number of products that are derived from mammals. However, many sensitized subjects can continue to eat red meat or dairy without overt allergic symptoms. A big question that requires further research is whether all patients with the syndrome should

avoid dairy because of the possible link with chronic inflammation of the arteries. We also need to better understand the risk of reactions to the wide variety of products that may include small amounts of material derived from mammals.

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ONLINE REPOSITORY

TABLE E1. Regions of the world where tick-acquired red meat allergy cases have been described and the relevant ticks that have been associated with α -Gal sensitization

Region/country	Tick	Notes
Australia	<i>Ixodes holocyclus</i>	Bites of this tick can cause anaphylaxis
United States	<i>Amblyomma americanum</i>	The larval stage of this tick, commonly called seed ticks, suspected to cause sensitization in many cases
Europe: Sweden, France, Italy, Spain, Germany	<i>Ixodes ricinus</i>	This tick can also carry the bacteria that causes Lyme disease
Asia: Japan, South Korea	<i>Haemaphysalis longicornis</i> <i>Amblyomma testudinarium</i>	The frequency of <i>A. testudinarium</i> bites has been shown to correlate with α -Gal sIgE levels
Central/South America: Panama	<i>Amblyomma cajennense</i> complex	A species within this complex, <i>A. sculptum</i> , has been shown to carry α -Gal
Africa: South Africa	?	Scores of challenge-proven cases, but no specific tick has been described to date