

Alpha-Gal Syndrome: Clinical Presentation, New Concepts, and Unmet Needs

Jörg Fischer, MD^{1,*}
Christiane Hilger, PhD²

Address

^{1,2}Department of Dermatology, Faculty of Medicine, Eberhard Karls University
Tübingen, Liebermeisterstr 25, 72076, Tübingen, Germany
Email: Joerg.Fischer@med.uni-tuebingen.de

²Department of Infection and Immunity, Luxembourg Institute of Health, Esch-
sur-Alzette, Luxembourg

Published online: 2 June 2017

© Springer International Publishing AG 2017

This article is part of the Topical Collection on *Anaphylaxis*

Keywords α -Gal · α -Gal syndrome · Anaphylaxis · Cetuximab · Pork kidney · Tick

Abbreviations α -Gal Galactose- α -1,3-galactose · IgE Immunoglobulin E · sIgE Specific IgE ·
IgG Immunoglobulin G · IgA Immunoglobulin A

Opinion statement

For decades, carbohydrate determinants were seen as cross-reactive structures without clinical impact. The discovery of specific IgE to the carbohydrate galactose- α -1,3-galactose, called α -gal, changed our perspective on the allergenic potential of carbohydrate determinants. α -Gal is present in tissues of non-primate mammals and, upon ingestion, can provoke a delayed form of allergic reaction in sensitized patients. We are faced with a new and unique entity of allergy with high clinical relevance in food allergy and anaphylaxis to drugs derived from mammalian products. Tick bites are assumed to constitute the primary sensitization source to α -gal. To address the complexity of this disease, the term α -gal syndrome has been suggested.

Introduction

The discovery of natural antigalactosyl IgG antibodies on thalassemic red blood cells in 1983 awakened the immunological interest in the carbohydrate galactose- α -1,3-galactose, called α -gal, as an antigen in humans [1]. In all mammals, except humans, apes, and Old World monkeys, the enzyme α -1,3-galactosyltransferase catalyzes the synthesis of the α -gal carbohydrate [2••]. Twenty to 28

million years ago, the gene coding for the α -1,3-galactosyltransferase was inactivated in ancestral Old World monkeys and apes as a unique evolutionary event [3]. According to fossil records in this period, an almost complete extinction of hominoids occurred [3, 4]. As several enveloped viruses, bacteria, and protozoa were found to express the α -gal epitope, it has been assumed

that the production of natural antibodies directed against the α -gal epitope could have provided an evolutionary advantage through immune protection against pathogens [2••]. In humans, anti- α -gal antibodies are found as IgG, IgM, and IgA isotypes and constitute with about 1% of immunoglobulins the most abundant human antibodies [5]. These antibodies represent a major immune barrier in xenotransplantation, i.e., transplantation of organs from pigs into humans [2••]. On the other hand, interesting advances have been made by using α -gal as an antigen for immunotherapy in wound healing, tissue regeneration, or cancer vaccine therapy [2••]. However, the approval of the drug cetuximab, a chimeric mouse-human IgG₁ monoclonal antibody directed against the epidermal growth factor receptor and used for the treatment of colorectal and squamous cell cancer, in the USA in 2003, brought up an aspect that has been overlooked for two decades. Shortly after launching, there were reports from southeastern US federal states of a high rate of hypersensitivity reactions on the first contact with cetuximab [6]. Chung et al. identified specific IgE antibodies directed at the α -gal carbohydrate as trigger of these hypersensitivity reactions. The epitope was located on the mouse Fab region of cetuximab [6]. Anti- α -gal-producing B cells can undergo isotype switching to produce specific IgE (sIgE) to α -gal which causes allergic reactions. In 2009, Collins and colleagues described a new form of delayed food allergy associated with IgE specific for α -gal [7]. Today, this allergy is seen as a new entity of disease with a high clinical relevance in the field of mammalian-derived food and drugs [8]. This allergy shows unique characteristics, challenging accepted

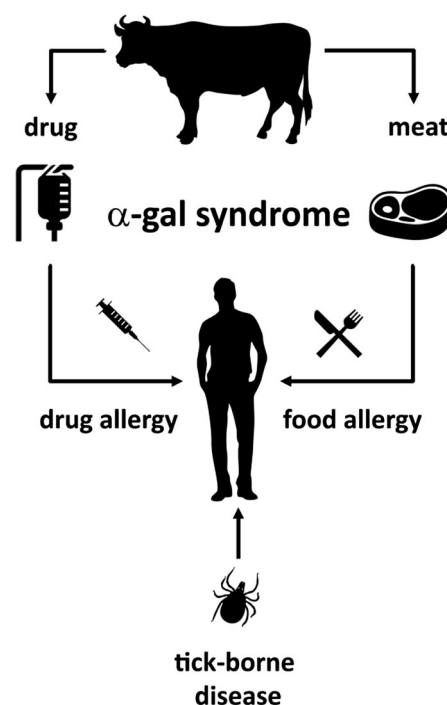


Fig. 1. The term α -gal syndrome describes a IgE-mediated immediate-type allergy to the disaccharide galactose- α -1,3-galactose (α -gal). Its classification as a syndrome was proposed as sIgE to α -gal can elicit different symptoms of varying severity, depending on the delivery route of α -gal. Drug allergy—administration of drugs derived from mammalian cells and tissue can induce drug allergy; food allergy—consumption of mammalian muscle meat and innards can induce food allergy; tick-borne disease—tick bites are currently the most likely pathway of IgE sensitization to α -gal in humans.

knowledge in allergology [9, 10]. The term α -gal syndrome was suggested to address the complexity of this disease (Fig. 1) [8, 11].

α -Gal syndrome—a food allergy with a unique pattern

Currently, the prevalence of the α -gal syndrome among food allergic individuals is not known, but sIgE positivity to α -gal ranges from 5.5 to 24.5% and it is a frequent finding in the general population [12–15]. While in Europe the α -gal syndrome is so far only observed in adults, in the USA it is also diagnosed in children and adolescents [11, 16]. The consumption of meat is a central part of the diet in industrial nations. In 2012, the estimated annual per capita consumption of beef and pork in the USA was 26.5 and 21.1 kg, respectively [17]. Delayed anaphylaxis to red meat is mainly reported upon ingestion of skeletal

muscle meat and innards from pork and beef, but it may also occur after eating any mammalian meat (Fig. 1).

Indeed, the consumption of mammalian meat and innards can elicit IgE-mediated type I reactions [7, 11, 18]. The clinical presentation of allergic reactions ranges from urticaria/angioedema to life-threatening anaphylaxis with hypotension, shock, and unconsciousness. In contrary to common experience with food allergy, the allergic reaction does not occur immediately after consumption, but with a delay of 3–6 h (delayed anaphylaxis) [7]. This delayed IgE-mediated anaphylaxis has to be distinguished from the immediate-type meat allergy where symptoms occur very rapidly (<1 h) after meat consumption, and IgE are directed against proteins. This is, for example, the case in pork-cat syndrome where IgE are directed against porcine serum albumin [19–22]. The time needed for the release of α -gal from glycoproteins and/or glycolipids during digestion and absorption is assumed to be responsible for the delayed onset of this type I allergic reaction [23•]. This process can be quantitatively and kinetically modulated by single factors, or a combination of endogenous and exogenous factors (e.g., alcohol, physical exercise, non-steroid analgesic, infections, and menstruation) [24]. According to the concept of food-dependent exercise-induced anaphylaxis (FDEIA), these cofactors are assigned a key role as a potential food allergen needs to reach a critical allergen concentration in the body capable of eliciting an allergic reaction. Oral challenge tests have shown that FDEIA is of high relevance for the α -gal syndrome [25]. It is possible that individuals having α -gal sIgE, but no evidence of allergic reactions to mammalian meat, can experience anaphylaxis upon exposure to mammalian meat in addition to relevant cofactors [25].

Based on clinical observations, the lowest-observed-adverse-effect levels (LOAEL) for allergic reactions after consumption of mammalian meat, innards, or sausages vary widely among affected individuals, but it is generally accepted that oral intake of trace quantities of α -gal does not elicit allergic reactions [11, 26, 27]. The content of α -gal in dairy products, cheese, and gelatin containing sweets is tolerated in a part of the patients, but not in highly allergic individuals [7, 27, 28]. Some patients with α -gal syndrome do not stop the consumption of mammalian meat; they only reduce the consumed amount of meat [27]. α -Gal content seems to vary between mammalian species [25, 27]. In particular, pork kidney and other innards elicit symptoms that are more severe and that occur within a shorter delay. Even a few grams of pork kidney (5–50 g) can elicit anaphylaxis, and the onset of an allergic reaction can occur as early as within 1 h after consumption [25, 29]. Recently, porcine angiotensin I-converting enzyme (ACE I) and aminopeptidase N (AP-N), both highly glycosylated proteins of urogenital tissues, were identified as major IgE-binding molecules in pork kidney [30]. Allergenic activity was confirmed to be dependent of the presence of α -gal epitopes.

Diagnosis of the α -gal syndrome strongly relies on clinical history and specific IgE determination. However, not all patients sensitized to α -gal will present clinical symptoms upon consumption of mammalian meat and IgE titers are not predictive of clinical reactivity. Due to the delayed reaction, food challenges are highly risky and should only be done in a clinical setting. Skin prick tests using meat extracts often give false-negative results whereas prick-to-prick tests with pork or beef kidney proved to be very sensitive [25]. Recently, successful desensitization has been reported in two patients [31].

α -Gal syndrome—a dangerous drug allergy

The high rate of hypersensitivity reactions upon intravenous administration of cetuximab, a therapeutic chimeric monoclonal antibody carrying an α -gal epitope, led to the discovery of α -gal sIgE [6] (Fig. 1). In Southeastern USA, about 20% of the treated oncologic patients developed anaphylaxis upon first contact with cetuximab, indicating a high risk of the drug in this region, compared to other US regions and Europe [32]. Although the particular risk related to cetuximab is known, until now treatment-related deaths occur [33]. The target of α -gal-specific IgE is located in the mouse Fab region of cetuximab. Some other therapeutic antibodies contain only α -galactosylated glycans in their Fc domains, but these are not recognized by α -gal sIgE-positive individuals (e.g., infliximab, palivizumab) [34••].

Antivenoms are formulations of divalent or monovalent immunoglobulin fragments (F(ab')₂/Fab) derived from mammalian plasma via fractionation and enzymatic digestion. The animals, in most cases sheep or horse, have been previously immunized with snake venom [35]. These therapeutics mitigate the progression of toxic effects by neutralization of snake venom components. Antivenoms were first developed in 1894 by the French scientists A. Clamette and C. Physalix/G. Bertrand and can be considered as the oldest therapeutic antibodies in medical history [35]. As a source of heterologous proteins, these drugs induce hypersensitivity reactions in approximately 20% of the patients [35]. Recently, the α -gal-epitope was identified as a potential target of IgE-mediated reactivity to antivenoms and as a possible cause of the high incidence of hypersensitivity reactions during the first application of antivenoms [36].

Gelatin is manufactured from the connective tissue of beef and pork, and it consists of hydrolyzed collagen. The collagen α -1 (VI) chain has been shown to carry an α -gal-epitope [37]. As this epitope is not denatured by the manufacturing process, it is one of the targets responsible for IgE-mediated reactivity to gelatin [38]. Gelatin is not only used in processed foods and sweets but also used in medicine as colloidal volume replacement agent and as stabilizer in some vaccines. Intravenous challenge tests have shown that gelatin colloid can elicit anaphylaxis in α -gal-sensitized individuals [38]. Recent reports have referred to α -gal-related anaphylaxis after vaccination and even anaphylaxis associated with a vaginal gelatin capsule [39–41]. The α -gal-related risk of vaccines warrants further analysis.

Bioprosthetic heart valves are manufactured from porcine and beef valve tissues. It is known that α -gal epitopes expressed on these xenogeneic tissues are capable to trigger hyperacute and acute vascular rejection phenomena due to IgG and IgM antibodies and that they are an important factor in bioprosthetic heart valve failure [42]. Neither glutaraldehyde fixation nor decellularization procedures ensure a completely masking or inactivation of α -gal epitopes [42]. A recent report discusses an association of α -gal sIgE in two patients with a premature degeneration of bioprosthetic aortic valves [43]. The related risk of rejection of bioprosthetic heart valves due to α -gal sIgE requires further monitoring.

There is little knowledge on tolerance of α -gal-containing drugs in α -gal sIgE-positive individuals. Basophil activation test (BAT) with cetuximab and antivenom showed CD63 upregulation in individuals with low α -gal sIgE levels and reported tolerance to mammalian meat and entrails [36]. Therefore, it is assumed that the delivery route of α -gal is crucial for the risk of an allergic reaction. Especially the

intravenous application of α -gal-containing drugs is associated with a high risk. Due to this potential risk, a special warning regarding the administration of α -gal-containing drugs may be needed in all individuals sensitized to α -gal, even if they are tolerant to mammalian meat and entrails. This general warning however warrants further assessment. Panitumumab can be used as safe substitute drug for cetuximab and dextran and hydroxyethyl starch as alternative colloidal volume replacement agents [44].

α -gal syndrome—a tick-borne disease

The fact that patients developed anaphylaxis on first contact with cetuximab indicated that the patients were presensitized, and research focused on an environmental factor responsible for the generation of α -gal sIgE [45]. In Australia, clinical observations showing a correlation between allergic local reactions to tick bites and allergy to red meat brought the attention on tick bites [46]. The finding that the prevalence of anaphylaxis to cetuximab was particularly high in the endemic area of the rocky mountain spotted fever, a tick-borne disease mainly transmitted by *Amblyomma americanum*, was another important step [45]. Till now, α -gal has been detected in various tick species, including *Amblyomma* spp., *Haemaphysalis longicornis*, and *Ixodes* spp. by ELISA and immunoblotting techniques [14, 45, 47] as well as by immunohistochemical staining of ticks [14, 45, 47]. Recently, it was shown that α -1,3-galactosyltransferase-deficient mice could be sensitized to α -gal by tick saliva of *Amblyomma sculptum* [48]. Therefore, it is commonly assumed that tick bites constitute the primary sensitization source to α -gal and α -gal syndrome can be considered as a tick-borne disease (Fig. 1). One likely hypothesis is that α -gal enters the tick during blood meals taken up from small mammals and then can be transferred to humans with the next blood meal which is necessary for the next step in the life cycle. This introduces the possibility of vector-borne allergies as a novel concept in allergology. Since the 1940s, there are sporadic reports of anaphylaxis to tick bites from all over the world [49–53•, 54]. In Australia, tick-induced anaphylaxis (TiA) is observed during removal of *Ixodes holocyclus* ticks [53•]. As this tick species produces a toxin causing paralysis of the host, further analysis is warranted to clarify whether the α -gal epitope or other allergens are responsible for these severe reactions. A typical phenomenon of tick bites in α -gal-sensitized individuals is local allergic reactions around the bites, presenting as erythematous papules or plaques itching for more than 10 days [45, 46]. The prevalence of these local reactions varies in different parts of the world. Whereas the phenomenon is frequent in Australia and the Southeastern USA, in Europe it seems to occur only during the summer months in years with favorable climatic conditions for ticks [55]. In tropical and subtropical areas, ticks can develop faster than in temperate climate zones and molt twice a year. It is conceivable that the development time from the nymph to adult stage is crucial for the concentration of remnants of α -gal-carrying mammalian proteins in tick hemolymph and the potential allergic risk of a tick bite. *Amblyomma americanum* is known for a rapid development from nymph to adult stage with a minimal period of only 3 weeks [56]. This can provide a possible explanation for the high prevalence of α -gal sIgE positivity in the general population in southeastern US federal states.

Conclusions

The α -gal syndrome is associated with the presence of sIgE to the carbohydrate α -gal. It has changed our perspective on the allergenic potential of carbohydrate determinants. Some carbohydrates can no longer be seen as cross-reactive structures without clinical relevance that we have to cope with in allergy diagnosis. We are faced with a new entity of allergy with unique immunological and clinical features. The topic is developing rapidly, but a number of questions remain unanswered. The mechanism of sensitization and the reason for the delayed allergic response upon consumption of mammalian meat are still to be elucidated. There is an increasing awareness of this new allergy syndrome, but it is suspected that it is currently underdiagnosed. Tick bites are assumed to constitute the primary sensitization source to α -gal. A tick bite can result in the loss of tolerance to mammalian meat, innards, or mammalian-derived drugs after safe consumption or administration for years. We still do not know the immunological key factors responsible for this loss of tolerance. Several clinical needs are still unmet. One of these is an improved and safe diagnostic test, which would allow the prediction of tolerance or risk of an allergic reaction to particular mammalian foods or mammalian-derived drugs. Also long-term follow-up data are needed from patients with α -gal syndrome. According to current knowledge, avoiding tick bites is the best strategy for prevention and treatment. In contrast to the initial observation, α -gal syndrome is not a disease limited to endemic areas, but a disease of global impact.

Compliance with Ethical Standards

Conflict of Interest

Dr. Jörg Fischer declares the he has conflicts of interest. Dr. Christiane Hilger declares the she has conflicts of interest.

Human and Animal Rights and Informed Consent

All cited studies with human subjects by any of the authors were approved by the responsible Ethics Commission and performed on informed consent of the participants. This article does not contain any study with animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. Galili U, Korkesh A, Kahane I, Rachmilewitz EA. Demonstration of a natural antigalactosyl IgG antibody on thalassemic red blood cells. *Blood*. 1983;61:1258–64.
 2. •• Galili U. Anti-gal: an abundant human natural antibody of multiple pathogeneses and clinical benefits. *Immunology*. 2013;140:1–11. doi:[10.1111/imm.12110](https://doi.org/10.1111/imm.12110).

Excellent review summarizing all facts of the human immune response to α -gal

3. Galili U, Clark MR, Shohet SB, Buehler J, Macher BA. Evolutionary relationship between the natural anti-Gal antibody and the Gal alpha 1—3Gal epitope in primates. *Proc Natl Acad Sci U S A*. 1987;84:1369–73.
 4. Galili U, Macher BA, Buehler J, Shohet SB. Human natural anti-alpha-galactosyl IgG. II. The specific recognition of alpha (1—3)-linked galactose residues. *J Exp Med*. 1985;162:573–82.
 5. Galili U, Rachmilewitz EA, Peleg A, Flechner I. A unique natural human IgG antibody with anti-alpha-galactosyl specificity. *J Exp Med*. 1984;160:1519–31.
 6. Chung CH, Mirakhur B, Chan E, Le Q-T, Berlin J, Morse M, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med*. 2008;358:1109–17. doi:10.1056/NEJMoa074943.
 7. Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, Lewis BD, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. *J Allergy Clin Immunol*. 2009;123:426–33. doi:10.1016/j.jaci.2008.10.052.
 8. Steinke JW, Platts-Mills TAE, Commins SP. The alpha-gal story: lessons learned from connecting the dots. *J Allergy Clin Immunol*. 2015;135:589–596; quiz 597. doi:10.1016/j.jaci.2014.12.1947.
 9. Platts-Mills TAE, Schuyler AJ, Erwin EA, Commins SP, Woodfolk JA. IgE in the diagnosis and treatment of allergic disease. *J Allergy Clin Immunol*. 2016;137:1662–70. doi:10.1016/j.jaci.2016.04.010.
 10. Commins SP, Jerath MR, Cox K, Erickson LD, Platts-Mills T. Delayed anaphylaxis to alpha-gal, an oligosaccharide in mammalian meat. *Allergol Int*. 2016;65:16–20. doi:10.1016/j.alit.2015.10.001.
 11. Fischer J, Biedermann T. Delayed immediate-type hypersensitivity to red meat and innards: current insights into a novel disease entity. *J Dtsch Dermatol Ges*. 2016;14:38–44. doi:10.1111/ddg.12821.
 12. Villalta D, Pantarotto L, Da Re M, Conte M, Sjolander S, Borres MP, et al. High prevalence of sIgE to galactose-alpha-1,3-galactose in rural pre-Alps area: a cross-sectional study. *Clin Exp Allergy*. 2016;46:377–80. doi:10.1111/cea.12655.
 13. Gonzalez-Quintela A, Dam Laursen AS, Vidal C, Skaaby T, Gude F, Linneberg A. IgE antibodies to alpha-gal in the general adult population: relationship with tick bites, atopy, and cat ownership. *Clin Exp Allergy*. 2014;44:1061–8. doi:10.1111/cea.12326.
 14. Hamsten C, Starkhammar M, Tran TAT, Johansson M, Bengtsson U, Ahlen G, et al. Identification of galactose-alpha-1,3-galactose in the gastrointestinal tract of the tick *Ixodes ricinus*; possible relationship with red meat allergy. *Allergy*. 2013;68:549–52. doi:10.1111/all.12128.
 15. Hamsten C, Tran TAT, Starkhammar M, Brauner A, Commins SP, Platts-Mills TAE, et al. Red meat allergy in Sweden: association with tick sensitization and B-negative blood groups. *J Allergy Clin Immunol*. 2013;132:1431–4. doi:10.1016/j.jaci.2013.07.050.
 16. Kennedy JL, Stallings AP, Platts-Mills TAE, Oliveira WM, Workman L, James HR, et al. Galactose-alpha-1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children. *Pediatrics*. 2013;131:e1545–52. doi:10.1542/peds.2012-2585.
 17. Maennel A. Meat atlas—facts and figures about the animals we eat. 1th ed. Berlin: Heinrich-Böll-Stiftung; 2014.
 18. Commins SP, James HR, Stevens W, Pochan SL, Land MH, King C, et al. Delayed clinical and ex vivo response to mammalian meat in patients with IgE to galactose-alpha-1,3-galactose. *J Allergy Clin Immunol*. 2014;134:108–15. doi:10.1016/j.jaci.2014.01.024.
 19. Morisset M, Arumugam K, Ollert M, Hilger C. Horse-meat allergy mediated by dog-allergy: a case report and review of the literature. *Allergo J Int*. 2016;25:76–81. doi:10.1007/s40629-016-0109-1.
 20. Hilger C, Kohnen M, Grigioni F, Lehnert C, Hentges F. Allergic cross-reactions between cat and pig serum albumin. Study at the protein and DNA levels. *Allergy*. 1997;52:179–87.
 21. Drouet M, Sabbah A. The pork/cat syndrome or crossed reactivity between cat epithelia and pork meat. *Monogr Allergy*. 1996;32:164–73.
 22. Posthumus J, James HR, Lane CJ, Matos LA, Platts-Mills TAE, Commins SP. Initial description of pork-cat syndrome in the United States. *J Allergy Clin Immunol*. 2013;131:923–5. doi:10.1016/j.jaci.2012.12.665.
 23. Commins SP, Jerath MR, Platts-Mills T. The glycan did it: how the α -gal story rescued carbohydrates for allergists—a US perspective. *Allergo J Int*. 2016;25:44–8. doi:10.1007/s40629-016-0097-1.
- Comprehensive text summing up the way how the α -gal syndrome was discovered
24. Wolbing F, Fischer J, Koberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy*. 2013;68:1085–92. doi:10.1111/all.12193.
 25. Fischer J, Hebsaker J, Caponetto P, Platts-Mills TAE, Biedermann T. Galactose-alpha-1,3-galactose sensitization is a prerequisite for pork-kidney allergy and cofactor-related mammalian meat anaphylaxis. *J Allergy Clin Immunol*. 2014;134:755–759.e1. doi:10.1016/j.jaci.2014.05.051.
 26. Commins SP. Invited commentary: alpha-gal allergy: tip of the iceberg to a pivotal immune response. *Curr Allergy Asthma Rep*. 2016;16:61. doi:10.1007/s11882-016-0641-6.
 27. Fischer J, Yazdi AS, Biedermann T. Clinical spectrum of alpha-gal syndrome: from immediate-type to delayed immediate-type reactions to mammalian innards and meat. *Allergo J Int*. 2016;25:55–62. doi:10.1007/s40629-016-0099-z.

28. Caponetto P, Fischer J, Biedermann T. Gelatin-containing sweets can elicit anaphylaxis in a patient with sensitization to galactose-alpha-1,3-galactose. *J Allergy Clin Immunol Pract*. 2013;1:302–3. doi:10.1016/j.jaip.2013.01.007.
 29. Morisset M, Richard C, Astier C, Jacquenet S, Croizier A, Beaudouin E, et al. Anaphylaxis to pork kidney is related to IgE antibodies specific for galactose-alpha-1,3-galactose. *Allergy*. 2012;67:699–704. doi:10.1111/j.1398-9995.2012.02799.x.
 30. Hilger C, Fischer J, Swiontek K, Hentges F, Lehnert C, Eberlein B, et al. Two galactose-alpha-1,3-galactose carrying peptidases from pork kidney mediate anaphylactogenic responses in delayed meat allergy. *Allergy*. 2016;71:711–9. doi:10.1111/all.12835.
 31. Unal D, Coskun R, Demir S, Gelincik A, Colakoglu B, Buyukozturk S. Successful beef desensitization in 2 adult patients with a delayed-type reaction to red meat. *J Allergy Clin Immunol Pract*. 2017; doi:10.1016/j.jaip.2016.12.008.
 32. O'Neil BH, Allen R, Spigel DR, Stinchcombe TE, Moore DT, Berlin JD, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *J Clin Oncol*. 2007;25:3644–8. doi:10.1200/JCO.2007.11.7812.
 33. Pointreau Y, Commins SP, Calais G, Watier H, Platts-Mills TAE. Fatal infusion reactions to cetuximab: role of immunoglobulin e-mediated anaphylaxis. *J Clin Oncol*. 2012;30:334; author reply 335. doi:10.1200/JCO.2011.38.4701.
 - 34.●● van Lammerts Bueren JJ, Rispens T, Verploegen S, van der Palen-Merkus T, Stapel S, Workman LJ, et al. Anti-galactose-alpha-1,3-galactose IgE from allergic patients does not bind alpha-galactosylated glycans on intact therapeutic antibody Fc domains. *Nat Biotechnol*. 2011;29:574–6. doi:10.1038/nbt.1912.
- This study provides an update on current findings on α -gal on therapeutic antibodies
35. Leon G, Herrera M, Segura A, Villalta M, Vargas M, Gutierrez JM. Pathogenic mechanisms underlying adverse reactions induced by intravenous administration of snake antivenoms. *Toxicon*. 2013;76:63–76. doi:10.1016/j.toxicon.2013.09.010.
 36. Fischer J, Eberlein B, Hilger C, Eyer F, Eyerich S, Ollert M, et al. Alpha-gal is a possible target of IgE-mediated reactivity to antivenom. *Allergy*. 2016; doi:10.1111/all.13073.
 37. Takahashi H, Chinuki Y, Tanaka A, Morita E. Laminin gamma-1 and collagen alpha-1 (VI) chain are galactose-alpha-1,3-galactose-bound allergens in beef. *Allergy*. 2014;69:199–207. doi:10.1111/all.12302.
 38. Mullins RJ, James H, Platts-Mills TAE, Commins S. Relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose. *J Allergy Clin Immunol*. 2012;129:1334–1342.e1. doi:10.1016/j.jaci.2012.02.038.
 39. Vidal C, Mendez-Brea P, Lopez-Freire S, Gonzalez-Vidal T. Vaginal capsules: an unsuspected probable source of exposure to alpha-gal. *J Invest Allergol Clin Immunol*. 2016;26:388–9. doi:10.18176/jiaci.0105.
 40. Stone CA Jr, Hemler JA, Commins SP, Schuyler AJ, Phillips EJ, Peebles RS Jr, et al. Anaphylaxis after zoster vaccine: implicating alpha-gal allergy as a possible mechanism. *J Allergy Clin Immunol*. 2016; doi:10.1016/j.jaci.2016.10.037.
 41. Pinson ML, Waibel KH. Safe administration of a gelatin-containing vaccine in an adult with galactose-alpha-1,3-galactose allergy. *Vaccine*. 2015;33:1231–2. doi:10.1016/j.vaccine.2015.01.020.
 42. Sung Jeong W, Jin Kim Y, Lim H-G, Jung S, Ryul LJ. The immune responses and calcification of bioprostheses in the alpha1,3-galactosyltransferase knockout mouse. *J Heart Valve Dis*. 2016;25:253–61.
 43. Hawkins RB, Frishtak HL, Kron IL, Ghanta RK. Premature bioprosthetic aortic valve degeneration associated with allergy to galactose-alpha-1,3-galactose. *J Card Surg*. 2016;31:446–8. doi:10.1111/jocs.12764.
 44. Caponetto P, Biedermann T, Yazdi AS, Fischer J. Panitumumab: a safe option for oncologic patients sensitized to galactose-alpha-1,3-galactose. *J Allergy Clin Immunol Pract*. 2015;3:982–3. doi:10.1016/j.jaip.2015.06.015.
 45. Commins SP, James HR, Kelly LA, Pochan SL, Workman LJ, Perzanowski MS, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. *J Allergy Clin Immunol*. 2011;127:1286–93.e6. doi:10.1016/j.jaci.2011.02.019.
 46. van Nunen SA, O'Connor KS, Clarke LR, Boyle RX, Fernando SL. An association between tick bite reactions and red meat allergy in humans. *Med J Aust*. 2009;190:510–1.
 47. Chinuki Y, Ishiwata K, Yamaji K, Takahashi H, Morita E. Haemaphysalis longicornis tick bites are a possible cause of red meat allergy in Japan. *Allergy*. 2016;71:421–5. doi:10.1111/all.12804.
 48. Araujo RN, Franco PF, Rodrigues H, Santos LCB, McKay CS, Sanhueza CA, et al. Amblyomma sculptum tick saliva: alpha-Gal identification, antibody response and possible association with red meat allergy in Brazil. *Int J Parasitol*. 2016;46:213–20. doi:10.1016/j.ijpara.2015.12.005.
 49. van Wye JE, Hsu YP, Terr AI, Moss RB, Lane RS. Anaphylaxis from a tick bite. *N Engl J Med*. 1991;324:777–8.
 50. Sanchez M, Venturini M, Blasco A, Lobera T, Bartolome B, Oteo JA. Tick bite anaphylaxis in a patient allergic to bee venom. *J Invest Allergol Clin Immunol*. 2014;24:284–5.
 51. Moneret-Vautrin DA, Beaudouin E, Kanny G, Guerin L, Roche JF. Anaphylactic shock caused by ticks (Ixodes ricinus). *J Allergy Clin Immunol*. 1998;101:144–5.
 52. Fernandez-Soto P, Davila I, Laffond E, Lorente F, Encinas-Grandes A, Perez-Sanchez R. Tick-bite-induced anaphylaxis in Spain. *Ann Trop Med Parasitol*. 2001;95:97–103.

53. • van Nunen S. Tick-induced allergies: mammalian meat allergy, tick anaphylaxis and their significance. *Asia Pac Allergy*. 2015;5:3–16. doi:[10.5415/apallergy.2015.5.1.3](https://doi.org/10.5415/apallergy.2015.5.1.3). Comprehensive text summing up the impact of tick bites in α -gal syndrome
54. Acero S, Blanco R, Bartolome B. Anaphylaxis due to a tick bite. *Allergy*. 2003;58:824–5.
55. Fischer J, Lupberger E, Hebsaker J, Blumenstock G, Aichinger E, Yazdi AS, et al. Prevalence of type I sensitization to alpha-gal in forest service employees and hunters. *Allergy*. 2017; doi:[10.1111/all.13156](https://doi.org/10.1111/all.13156).
56. Estrada-Pena A, de la Fuente J, Cabezas-Cruz A. A comparison of the performance of regression models of *Amblyomma americanum* (L.) (Ixodidae) using life cycle or landscape data from administrative divisions. *Ticks Tick Borne Dis*. 2016;7:624–30. doi:[10.1016/j.ttbdis.2016.01.010](https://doi.org/10.1016/j.ttbdis.2016.01.010).