Galactose-Alpha-1,3-Galactose, Mammalian Meat and Anaphylaxis: A World-Wide Phenomenon?

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Opinion Statement

Mammalian meat allergy following tick bites is known to occur in Australia, North America, Europe, Asia, Africa and Central America. Over the last decade, the condition has become increasingly prevalent in tick-endemic areas of Australia and the USA. In mammalian meat-allergic individuals, gelatine allergy and/or cow's milk allergy may co-exist. Awareness of tick-induced allergies in health professionals and the general community is key to both a timely diagnosis and the prevention of mammalian meat allergy. Treatment of mammalian meat allergy is limited currently to avoidance of all mammalian meat, whilst gelatine allergy similarly mandates avoidance of mammalian-derived gelatine, especially intravenously administered gelatine-containing solutions. Adults with anaphylaxis to mammalian meat should have a convalescent tryptase estimation and investigations for mastocytosis should then be undertaken if the tryptase is significantly elevated. Before initiating treatment with certain therapeutic agents (e.g. cetuximab, gelatine-containing substances, bovine artificial blood), a careful assessment of the risk of anaphylaxis, including serological analysis for galactose-alpha-1,3-galactose-specific immunoglobulin E, should be undertaken in any individual who works, lives, volunteers or participates in leisure activities in a tick-endemic area, particularly where a history is obtained of a tick bite prior, or of mammalian meat or gelatine allergy. Strategies aimed at the prevention of tick bites are paramount for primary prevention and amelioration of mammalian meat allergy.

Key points

1. Mammalian meat allergies are characterised by delayed anaphylaxis, urticaria and angioedema, occurring 2–10 h after the ingestion of mammalian meat and are commonly preceded by a tick bite.
2. Mammalian meat allergy may be confirmed by galactose-alpha-1,3-galactose and

mammalian meat-specific immunoglobulin E estimations, cetuximab skin testing or skin prick testing with fresh, raw, organic meat extracts.

3. Confirmation of gelatine allergy requires intradermal testing if skin prick testing is negative and gelatine-specific immunoglobulin E is not detected.

4. Dietary exclusion of mammalian meat, mammalian gelatine and cow's milk products, as indicated by the individual clinical sensitivity profile, is the mainstay of treatment in allergy to galactose-alpha-1,3-galactose.

5. Mammalian meat-allergic patients should be aware of the risk of allergic reaction to cetuximab, gelatine and mammalian meat-containing therapeutic agents and health supplements and to check the ingredients carefully.

6. Search for co-existing mastocytosis when tryptase levels are elevated in convalescence.

7. Prevention of tick bites appears to limit the duration of the condition in some individuals and is essential to the primary prevention of mammalian meat allergy.

Introduction

On 27 November 2007, an abstract by van Nunen et al. entitled "The Association between *Ixodes holocyclus* tick bite reactions and red meat allergy" was published online in the *Internal Medicine Journal* in the proceedings of the Australasian Society of Clinical Immunology and Allergy (ASCIA) 18th Annual Scientific Meeting (ASM) held in Fremantle, Australia earlier that month [1]. The authors described 25 adult patients with positive skin prick tests and/or red meat-specific immunoglobulin (Ig)E detectable in their serum, 23 of whom had had allergic reactions following the ingestion of red meat (severe anaphylaxis after ingestion of red meat had occurred in 14/23). 24/25 patients had a history of tick bite. The authors postulated an association between the history of prior tick bite and the development of red meat allergy. This work was later published in a slightly expanded form in the *Medical Journal of Australia* in May 2009 [2].

On the other side of the world, again in 2007, O'Neil and colleagues had reported a 22 % incidence of grade 3 or 4 hypersensitivity reactions to cetuximab infusion in their patients in Tennessee and North Carolina when compared with an incidence of <3 % nationally and internationally [3]. Following on from this observation, in March 2008, Chung and colleagues published their work wherein they identified specific IgE directed against galactose- α -1,3-galactose (alphagal) as the cause of cetuximab-induced anaphylaxis [4]. In this paper, the authors referred to a series of patients (number unspecified) with IgE antibodies against alphagal who reported having had episodes

of anaphylaxis or severe angioedema 1–3 h after eating beef or pork. They speculated that the environmental exposures that may have determined the regional variability seen in cetuximab anaphylaxis might be due to histoplasmosis, amoeba, ticks, coccidiomycosis, nematodes or cestodes [4]. Commins et al. presented these data separately as an abstract at the American Academy of Allergy Asthma and Immunology (AAAAI) meeting in March 2008, reporting 10 patients with recurrent anaphylaxis and angioedema triggered by exposure to beef and pork, all of whom possessed alphagal-specific IgE [5]. Fortuitously, in the same poster area, Dr Raymond Mullins, who had attended the 2007 ASCIA ASM, as the then President-elect of ASCIA, was presenting his work on the clinical significance of sensitisation to gelatine colloids in 800 patients, some of whom were co-sensitised to mammalian meats [6].

In February 2009, Commins et al. reported 24 patients with delayed anaphylaxis, angioedema or urticaria after consumption of red meat who possessed IgE specific for alphagal [7]. They noted "Interestingly, more than 80 % of the patients in the present cohort report being bitten by ticks before having symptoms; a similar scenario has been recently described in a group of Australian patients" and referenced the 2007 abstract by van Nunen et al. [7].

Since then, Platts-Mills, Commins and co-workers, [4, 5, 7–10, 11•, 12, 13•, 14–16, 17••, 18•, 19] together with our colleagues around the world, [1, 2, 6, 9, 11•, 16, 18•, 20, 21•, 22•, 23, 24•, 25, 26, 27••, 31–35] have gathered extensive data and provided elegant proofs of the clinical

observation by van Nunen et al. [1] that tick bites are associated with the development of mammalian meat allergy. Their work has provided us with extraordinary and

continuing opportunities to learn about a clinically unique allergen and to gain fascinating insights into pivotal mechanisms of allergen sensitisation.

Reports from around the world of mammalian meat allergy associated with prior tick bites

As ticks are widely distributed around the world it is not surprising that mammalian meat allergy after tick bites has been reported in several countries other than Australia and the USA. The intriguing fact is not that there have been so many reports, but that the number of cases documented in other countries has been so few.

Europe

France

In France in 2009, Jacquenet and colleagues documented two cases of mammalian meat-induced anaphylaxis and confirmed by cetuximab skin testing that these patients were sensitised to alphagal [18]. Their group later presented an abstract at the 2012 AAAAI Meeting by Renaudin et al. describing six alphagal-positive patients with delayed urticaria and angioedema due to mammalian meat allergy [20]. Fourteen patients were described from France in 2012, all allergic to pork or beef kidney, all of whom tested positive for skin tests with cetuximab and for alphagal-specific IgE in their serum [21•]. Information regarding exposure to ticks was not included in these series. Morisset et al. at the EAACI-WAO meeting in Milan in 2013, described an additional single case in whom yoghurt allergy and ricotta cheese anaphylaxis developed after a repeat tick bite in a patient with previously established mammalian meat anaphylaxis confirmed by detection of alphagal-specific IgE in the serum [22•].

Spain

Nunez et al. in 2011 reported five patients from Spain with delayed mammalian meat-induced anaphylaxis [23]. All patients had positive beef and cetuximab skin tests, all had demonstrable beef-, lamb- and pork-specific IgE and all but one reported previous tick bites. The predominant tick species in the area of Spain where their patients lived is *Ixodes ricinus* [23].

Germany

In their case report of delayed anaphylaxis following ingestion of gelatine-containing sweets in a patient sensitised to alphagal, Caponetto and colleagues noted that they care for 21 patients in all with red meat anaphylaxis [24•]. In addition, Commins and Platts-Mills [8] have commented that Jappe is said to have identified patients with mammalian meat allergy and cetuximab and alphagal-specific IgE via serological studies and referenced her review of the topic [25].

Switzerland

In late 2013, in Switzerland, Michel and co-workers published online their study of two patients with mammalian meat allergy, noting that skin prick tests and intradermal tests with cetuximab were positive in both, as were basophil activation tests [26].

Sweden

Hamsten and colleagues reported initially five patients with mammalian meat-induced anaphylaxis who had presumed exposure to *I. ricinus*, which is common in the greater Stockholm area [27••]. All five patients possessed alphagal-specific IgE [27••]. This series was later expanded and they have now described 39 patients with mammalian meat allergy and IgE against alphagal [9].

Korea

A single male patient aged 67 years with delayed pork and beef anaphylaxis and delayed urticaria after ingesting lamb was described by Lee et al. in 2012 [32, 33]. The diagnosis was confirmed by intradermal cetuximab skin testing [32, 33].

Japan

In Japan in 2012, Sekiya and colleagues reported a single case, a woman aged 74 years, who after a tick bite developed mammalian meat and cow's milk anaphylaxis confirmed by an oral challenge with pork [31].

Central America

The first four cases in Central America of delayed meat allergy with alphagal positivity were reported by Wickner and Commins in abstract form at the AAAAI Meeting in March 2014 [10]. The tick involved in sensitisation is thought most likely to be *A. cajennense* [10, 34].

As far as the author is aware, no cases have yet been reported from South America; however, *Ixodidae* (ticks) are known to be present and three species frequently parasitise humans: *A. neumanni* in 46 known localities in Argentina, *A. triste* in 21 known sites in Uruguay and *A. parvum* in 27 known areas in Argentina-Brazil, with *Ixodes* species virtually unknown to infest humans in South America (a single report from the entire continent) [34].

Two people who have lived all of their lives in a farming community near the coast in the Republic of South Africa have contacted the author regarding their long-standing mammalian meat allergies after tick bites that appeared in adulthood, and one of these patients has a gelatine allergy as well. One person from Costa Rica in Central America has also informed the author of her mammalian meat allergy, which she believes has followed tick bites.

In both Australia and the USA, however, large numbers of patients with mammalian meat allergy following tick bites have been identified [8]. In her practice alone, van Nunen has diagnosed over 500 patients (between 1985 and March 2014, with the great majority having presented from 2003 onwards) within a referral base of 440,000 people (1/880), which includes the tick-endemic areas nearby. She currently diagnoses an average of two

people per week with the complaint and in these tick-endemic areas to the north of Sydney, Australia, a diagnosis in adults of mammalian meat allergy, commonly anaphylaxis, appears to be as prevalent (estimate 0.12 % and higher when patients are included who have been diagnosed by other clinical immunologists in the same referral area) as the most common food allergy in adults requiring adrenaline worldwide, i.e. peanut allergy at 0.1 % [38]. Commins and colleagues are aware of in excess of 1,000 individuals with mammalian meat allergy after tick bites (1/8,000) in Virginia alone (population over 8 million) and have estimated that in the south-eastern states of the USA in excess of 5,000 people have the complaint [39]. The actual prevalence figures are likely to be higher in both Australia and the USA if the case frequency was estimated only in the sub-population of those who live in the tick hyper-endemic areas.

The most reasonable explanation for the increasing prevalence of mammalian meat allergy in both Australia and the USA is an increase in host numbers (bandicoots and other small native mammals flourishing in Australia and the increase in the white-tailed deer population in south-eastern USA) [12].

These contributions to defining the clinical spectrum of mammalian meat allergy associated with prior tick bites are summarised in Table 1.

Other relevant clinical findings in mammalian meat allergy following tick bites

Gelatine allergy and mammalian meat allergy

Gelatine allergy in children

Sensitisation to both beef and pork gelatines has been described in milk and meat-sensitised children [40]. Bogdanovic and colleagues reported 21/130 (16 %) children with beef-specific IgE and 44/116 (38 %) with pork-specific IgE had cross-reactive IgE to gelatine present, whilst 97 % were also sensitised to cow's milk [40]. It is interesting to note that this series of patients was recruited in Maryland, USA, within the known distribution for *A. americanum*. Gelatine has been added as a stabiliser to several vaccines and reports of anaphylaxis to vaccines on the basis of gelatine allergy have been documented by a number of workers including Kelso and others (MMR) [41], and Sakaguchi et al. to vaccines (MMR, varicella, Japanese encephalitis) and to gelatine-containing foods [42]. Sakaguchi and colleagues separately reported their findings in 10 children who had suffered an anaphylaxis to vaccines containing bovine gelatine [43]. In the majority of these children, their IgE also bound to kangaroo and mouse gelatine and this binding was completely inhibited by bovine gelatine, whereas reciprocal inhibition was incomplete, leading the authors to conclude that cross-reactivity between the mammalian gelatine was operative [43].

Gelatine allergy in adults with mammalian meat allergy and detection of alphaGal in gelatine and bovine products

Whilst avoidance of mammalian meat per se can be accomplished reasonably easily by our patients after advice from a dietitian fully versed in mammalian meat avoidance, those who have clinical sensitivity to gelatine have

Table 1. Contributions to defining the clinical spectrum of mammalian meat allergy after tick bites

Year	Authors	No. of patients	Tick species	Country	Contributions to clinical spectrum definition
2007	van Nunen et al. [1]	25	<i>Ixodes holocyclus</i>	Australia	Described occurrence in adults Described association with previous tick bites Described large local reactions at the site of the tick bites Described frequency of beef>lamb>pork>game skin prick tests Used raw organic meats for skin prick tests Described patients with multiple meat sensitisations Described skin prick test positivity with kangaroo, goat, venison and rabbit Described specific immunoglobulin E presence for beef, mutton and pork
2008	Commins et al. [5]	10	–	USA	Described alphagal as the epitope Documented the typically delayed nature of the response Confirmed use of raw organic meats suitable for skin prick tests Documented a lack of immunoglobulin E specific for poultry and fish Described serum immunoglobulin E specific for cat, dog and cow's milk (similar levels of cat and dog) Determined the cat-specific immunoglobulin E was not directed against Fel d1
2008	Mullins [6]	16	–	Australia	Described gelatine as an allergen in mammalian meat allergy Documented anaphylaxis due to gelatine-containing colloid in red meat allergy Documented oral gelatine allergic reactions in mammalian meat-allergic patients Noted intradermal testing required to detect sensitisation
2009	Commins et al. [7]	24	<i>Amblyomma</i> genus	USA	Confirmed alphagal as the epitope Noted only a 2- to 3-year history since onset of allergic reactions Noted symptoms occurred after cow's milk in almost half Noted ability of patients to tolerate small amounts of meat Previous tick bite history noted in great majority Quantitated amount of alphagal in fresh and skin prick test reagents Reported exercise as a co-factor within 2 h after beef Documented fewer or lack of reactions with avoidance Demonstrated no difference between commercial

Table 1. (Continued)

Year	Authors	No. of patients	Tick species	Country	Contributions to clinical spectrum definition
2009	van Nunen et al. [2]	25	<i>Ixodes holocyclus</i>	Australia	and conventional prick-prick tests Demonstrated superior results with fresh meat extracts Additional information: no patient with mammalian meat allergy had tick anaphylaxis
2009	Jacquetet et al. [20] Renaudin et al. [21]	2 6	–	France	Confirmed delayed reactions most common Confirmed alphagal as the epitope and occurrence of delayed urticarial and angioedema Used cetuximab intradermal testing Showed raw meat (beef, rabbit) skin prick test gave a larger result Described offal skin prick test positivity Added horse to list of mammalian meats Noted allergic reaction did not invariably occur after ingestion Noted low levels of meat-specific immunoglobulin E may explain above
2011	Nunez et al. [24]	5	<i>Ixodes ricinus</i>	Spain	Documented tick bites in mammalian meat allergy in Europe Documented alphagal positivity in Europeans with mammalian meat allergy Documented use of cetuximab as a skin prick test agent Verified utility of fresh, raw meat extracts for a skin prick test
2012	Sekiya et al. [30]	1	–	Japan	Reported a case of mammalian meat anaphylaxis after tick bite Recorded a mammalian meat-allergic patient who also had anaphylaxis to cow's milk (beef had also provoked anaphylaxis) Cetuximab-specific immunoglobulin E elevated Confirmed the diagnosis of delayed mammalian meat anaphylaxis by open oral challenge with pork
2012	Morisset et al. [22•]	14	–	France	Documented reactions to offal in mammalian meat allergy Challenge confirmation obtained in a small number of patients Confirmed exercise as a co-factor Documented alcohol as the most common co-factor Demonstrated offal had a higher concentration of alphagal Demonstrated co-factors likely to bring forward reactions
2012	Mullins et al. [11]	40	<i>Ixodes holocyclus</i>	Australia	Majority of patients co-sensitised to mammalian meat and gelatine Recorded clinical reactivity in mammalian meat allergy to both intravenous and oral gelatine

Table 1. (Continued)

Year	Authors	No. of patients	Tick species	Country	Contributions to clinical spectrum definition
2013	Caponetto et al. [25•]	21	<i>Ixodes ricinus</i>	Germany	<p>Noted gelatine allergy may be the initial presentation of mammalian meat allergy</p> <p>Reported a small number of patients with gelatine tests positive and mammalian meat tests negative who reacted to gelatine challenge and who remained free of anaphylaxis avoiding meat and gelatine</p> <p>Documented alphagal presence in gelatine and bovine products</p> <p>Confirmed persistent reactions may occur at tick bite site</p> <p>Confirmed foods containing gelatine can provoke anaphylaxis in mammalian meat allergy</p> <p>Confirmed that intra-cutaneous testing may be required to detect gelatine sensitisation</p> <p>Reported a reaction to ingested gelatine delayed by 10 h</p> <p>Demonstrated variability in severity between meats and offal</p> <p>Confirmed exercise as a co-factor</p> <p>Noted that repeatedly elevated tryptase levels in the absence of mammalian meat ingestion became normal after meticulous exclusion of dietary gelatine as well as mammalian meat</p>
2012	Lee et al. [31, 32]	1	–	Korea	<p>Confirmation of a case of delayed mammalian meat anaphylaxis (beef and pork) with cetuximab intradermal testing</p>
2013	Hamsten et al. [29••]	5	<i>Ixodes ricinus</i>	Sweden	<p>Confirmed alphagal-specific immunoglobulin E presence in mammalian meat allergy</p> <p>Confirmed beef-specific immunoglobulin E presence</p>
2013	Morisset et al. [23•]	1	<i>Ixodes ricinus</i>	France	<p>Reported a case of cow's milk product anaphylaxis (yoghurt and cheese) in mammalian meat allergy</p> <p>Documented cow's milk product reactions occurred after mammalian meat avoidance and following a further tick bite</p>
2013	Hamsten et al. [9]	39	<i>Ixodes ricinus</i>	Sweden	<p>Documented moose as another mammalian meat capable of provoking mammalian meat allergy</p>
2014	Michel et al. [27]	3	–	Switzerland	<p>Confirmed utility of cetuximab skin testing</p> <p>Examined basophil activation test utility</p>
2014	Wickner and Commins [10]	4	<i>Amblyomma cajennense</i>	Central America	<p>Documented delayed mammalian meat allergy and alphagal positivity</p> <p>Described another tick species</p> <p>Represents a potential model for the natural history of the condition</p>
- means 'not stated'					

benefited greatly from the work by Mullins et al. showing the presence of alphagal in gelatine and bovine products [11•]. Their findings now underpin our advice to patients regarding the risks of reacting to gelatine, in particular, as this can be administered intravenously in therapeutic preparations, e.g. gelatine-containing colloids, a route of administration that increases the possibility of anaphylaxis [11•]. Mullins et al. also noted gelatine allergy may be the initial presentation of mammalian meat allergy, recorded clinical reactivity in mammalian meat allergy to both intravenous and oral gelatine, reported a small number of patients with positive gelatine tests and negative mammalian meat tests who reacted to gelatine challenge and who remained free of anaphylaxis avoiding both mammalian meat and gelatine, and noted an historical association between tick bite exposure, sensitisation and allergy to red meat. The patients reported, from Canberra (and across to the Pacific coast), Australian Capital Territory, Australia, were exposed to *Ixodes holocyclus* [11•].

Mammalian meat allergy in children

Kennedy and colleagues identified 45 children from Virginia, USA, who had both a clinical history consistent with mammalian meat-induced delayed anaphylaxis or recurrent urticaria and IgE antibody specific for alphagal. All patients had a history of tick bite prior to alphagal detection, 39 of the 45 had evidence for persistent reactions to tick bites [13•]. This finding of local reactivity is in keeping with the fact that 24/25 patients in van Nunen's study had large local reactions at the site of their tick bites [1, 2] and Caponetto et al. noting persistent reactions at the bite site [24•]. Absorption studies in three sera determined that the cow's milk-specific IgE detected was entirely the result of alphagal in the cow's milk and these findings led Kennedy and co-workers to recommend alphagal testing and a search for mammalian meat allergy in those with a new diagnosis of cow's milk allergy who were aged over 5 years and living in tick-endemic areas. In general, the authors concluded mammalian meat allergy in children is not uncommon and that it mirrors their experience in adults [13•].

The clinical features of mammalian meat allergy, which can include gelatine allergy and/or cow's milk allergy, are now well defined and are known to affect both adults and children.

Treatment

- Patients with mammalian meat allergy associated with tick bites present with allergic reactions after ingesting mammalian meat, which are typically delayed [2, 5, 7, 13•, 31–33].
- The clinical spectrum comprises anaphylaxis in up to 60 % [1, 2] of individuals, delayed urticaria or angioedema [5, 7], or gut-related symptoms.
- Delay after mammalian meat ingestion is in the range of 2–10 h [5, 23].

- The mainstay of treatment in mammalian meat allergy is avoidance of mammalian meat and gelatine and cow's milk products where necessary.

Treatment of the acute phase of the allergic reaction

- Treatment of the acute phase of the allergic reaction does not differ from the treatment of anaphylaxis, urticaria, angioedema or gut reactions resulting from exposure to other allergens. Treatment of acute anaphylaxis relies upon adrenaline use as specified in all authoritative guidelines [14, 44, 44], and other clinical manifestations are treated with supportive or symptomatic treatment, e.g. antihistamines for urticaria.
- Completion of a record of events for several hours prior to the anaphylaxis is an important part of the management of an acute allergic reaction [15].
- Provision of an adrenaline auto-injector, together with education of the patient regarding the use, indications and contraindications for its use, provision of anaphylaxis action plans and a travel plan, issue of material illustrating its use (e.g. a DVD), a demonstration by the patient of their proficiency in the use of the device and the completion of online training in administration before they leave the emergency facility or as soon as is practicable is essential [44].

Treatment in the convalescent phase of the allergic reaction

- Pharmacological treatment in the convalescent phase of the allergic reaction is aimed at relieving residual discomfort resulting from the allergic reaction, e.g. antihistamines for ongoing pruritus and oral corticosteroids to limit any further swelling with angioedema.
- Supportive measures, such as administration of intravenous fluids (non-gelatine-containing) for dehydration as a result of gut involvement, may be required.
- In the convalescent phase of a reaction, historical evidence for the allergic-provoking factor should be sought, ideally commencing with an event record completed by the patient and their family whilst the events remained vivid, proceeding from immediately prior to the onset of the allergic reaction and extending for up to 12–24 h retrospectively. A history of mammalian meat ingestion some hours beforehand will be forthcoming in mammalian meat allergy. Occasionally, the initial episode in mammalian meat allergy will have been provoked by ingestion of gelatine-containing foods or cow's milk products (often soft cheeses) [11•].
- Search for co-existing mastocytosis where severe anaphylaxis has occurred and convalescent tryptase levels are elevated [35].

- Patients may have allergic reactions, including their initial episode, far from home. Even in non-tick-endemic areas, questioning should include a search for mammalian meat ingestion, particularly when the patient has presented with an otherwise unexplained anaphylaxis 'in the middle of the night' and tick exposure is possible a result of where they live (even if intermittently, e.g. the family holiday home), work, attend school, volunteer or participate in leisure activities [16].

Confirmation and characterisation of the mammalian meat allergy underpins treatment

- Confirmation of a diagnosis of an allergic reaction due to mammalian meat involves serological testing for alphagal-specific IgE and mammalian meat-specific IgE [7, 24, 27, 28••].
- When gelatine allergy is suspected, intradermal testing is indicated if gelatine-specific IgE is absent and skin prick testing is negative to gelatine [6, 11•].
- In the absence of the availability of alphagal-specific IgE testing, then cetuximab intradermal testing [20, 26, 29••, 31] or cetuximab skin prick testing [23] is useful.
- Skin prick testing with extracts of raw organic meats and prick-prick tests with raw meats have also been used to confirm the diagnosis [2, 7, 18, 20]. Skin prick testing with mammalian meats is characteristically small and its significance may be missed by both patient and physician if they are unfamiliar with this fact [7, 13•].
- The vast majority of mammalian meat-allergic patients have a history of a previous tick bite. Occasionally, the evidence for such a tick bite can be subtle, e.g. an excoriated scalp lesion consistent with a tick bite after even a single visit to a tick-endemic area without a tick being found in situ or the tick bite may only be recalled by another family member [16].
- Many patients with anaphylaxis have experienced large local or persistent reactions at the site of previous tick bites. [1, 2, 13•, 24•, 34]
- The role of co-factors in the provocation of an anaphylaxis is well recognised in mammalian meat allergy [7, 21•, 24•]. A careful search for these, particularly for exercise where the anaphylaxis has occurred within 2 h of ingestion of the mammalian meat, is often rewarding [7, 21•, 24•]. Other co-factors have been observed to amplify the reactions including alcohol [21•]. The role of co-factors may well offer an explanation of the observations made by many of our patients that they do not react every time they eat mammalian meat, particularly when they exhibit a low level of sensitisation [20].
- The safety of mammalian meat-allergic patients is improved when they understand the role of co-factors in determining whether or not they will suffer an anaphylaxis on any given occasion after ingestion of mammalian meat. It is useful, especially when a severe anaphy-

laxis has occurred, to state the obverse of “they may not react every time”, i.e. “that they may react on any occasion after ingesting mammalian meat”.

- Certainly, many mammalian meat-allergic individuals will tolerate small amounts of mammalian meat and if this has been their experience repeatedly, then continued ingestion of such amounts does not appear to result in a worsening of the allergic reactions.
- Following confirmation of a diagnosis of mammalian meat allergy, a medical alert device should be offered to avoid reactions to intravenous gelatine especially in those sensitised, to warn against the use of artificial bovine blood and document the mammalian meat anaphylaxis for travellers.

Dietary exclusion is the mainstay in treating mammalian meat allergy

- Avoidance of mammalian meat in the diet is of proven benefit in those with anaphylaxis after ingestion of mammalian meat [7, 11•, 13•, 34]. In those with a stable pattern of delayed urticaria, it may be possible for them to reduce the amounts they consume, be consistent with cooking methods and remain eating some mammalian meat. When angioedema is the clinical manifestation of mammalian meat allergy, exclusion is usually practiced, as patients are more intolerant of episodes of angioedema owing to their perception of unsightliness and the limitation of function that may occur. Gut symptoms can be severe and in this situation dietary exclusion is also often preferred by the patient.
- Prescription of a mammalian meat-free diet is ideally given by a dietitian familiar with the pitfalls experienced by mammalian meat-allergic patients [44].
- Dietary adequacy of iron and vitamin B₁₂ following the prescription of a mammalian meat-free diet is ensured by a meticulous review by the dietitian [44].
- Warnings regarding the increased propensity of offal meats (because of higher alphagal levels) to cause more severe reactions [21•], the ingestion of more exotic meats in one’s homeland (e.g. kangaroo, buffalo and venison in Australia, wild boar in Europe, bear and squirrel in the USA) and the ingestion when abroad of mammalian meats that are readily available in the country visited but not usually eaten at home by the tourist (e.g. guinea pig in South America).
- Avoidance of dietary gelatine likewise requires specialist dietetic advice as the range of foods containing mammalian-derived gelatine is wide: [11•].

Role of the physician, pharmacist and health supplement purveyors in patient safety

- Both physicians and pharmacists need to inform mammalian meat-

allergic patients of the risks inherent in taking cetuximab [4, 17••] as fatal reactions have occurred with its use [17••]. Sources of gelatine in therapeutic agents should be flagged, e.g. in vaccines, capsules, tablets and suppositories and in collagen-containing agents (implants).

- Physicians, pharmacists and health supplement purveyors need to be aware of the implications of any mammalian meat-derived contents of proprietary products, e.g. bovine colostrum.
- Regulatory authorities need to be cognizant of mammalian meat allergy in delineating disclosure rules for proprietary substances.

Prevention of tick bites: a role in the prevention and remission of the condition?

- Clearly, tick bite avoidance seems prudent in mammalian meat allergy, as tick bites have a pivotal role in sensitising the patient to mammalian meat [18••, 18•, 27••, 45•]. In some patients, there exists serological evidence that their sensitisation may be waning and a minority of individuals have, over time, had a remission in their allergy to mammalian meat [13•]. In addition, there is some evidence for the spectrum of clinical sensitivity expanding following a further tick bite [22•].
- Mammalian meat allergy offers an unparalleled opportunity for the primary prevention of allergy. Web-based awareness in tick-endemic communities of the potential for tick bites to provoke tick-induced allergies is key [44, 46–49]. Furthermore, knowledge of the management of ticks in endemic areas allows risk reduction by habitat modification; tick bites may be prevented by the provision of patient and community information regarding tick management measures and tick removal techniques suitable for allergy minimisation can be made more practicable for those living or working in tick-prone areas [44, 47].
- Prevention strategies for tick bites comprise behavioural changes in the human host informed by our knowledge of the biology of ticks, use of appropriate tickicidal-treated clothing and the use of repellents proven to reduce the number of tick bites [44, 47–49].

Emerging therapies

- Omalizumab is currently being trialled in carefully selected patients with severe morbidity from mammalian meat allergy (personal communication, Dr Karl Baumgart, Sydney, Australia).

Paediatric considerations

- Whilst the literature has mainly reported adults with mammalian meat allergy, it is important to note this condition also occurs in children [13•].

Compliance with Ethics Guidelines

Conflict of Interest

Sheryl van Nunen declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published in the preceding three years, have been highlighted as:

- Of importance
- Of major importance

1. van Nunen SA, Fernando SL, Clarke LR, Boyle RX. The association between *Ixodes holocyclus* tick bite reactions and red meat allergy. *Intern Med J*. 2007;37 Suppl 5:A132. doi:10.1111/j.1445-5994.2007.01551.x.
 2. van Nunen SA, O'Connor KS, Fernando SL, Clarke LR, Boyle RX. An association between tick bite reactions and red meat allergy in humans. *Med J Aust*. 2009;190:510–1. <https://www.mja.com.au/journal/2009/190/9/association-between-tick-bite-reactions-and-red-meat-allergy-humans>.
 3. 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.
 4. Chung CH, Mirakhor B, Chan E, Le QT, Berlin J, Morse M, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med*. 2008;358(11):1109–1117. doi: 10.1056/NEJMoa07943.
 5. Commins S, Lucas J, Hosen J, Satinover SM, Borish L, Platts-Mills TAE. Anaphylaxis and IgE antibodies to galactose-alpha-1,3-galactose (alphaGal): insight from the identification of novel IgE ab to carbohydrates on mammalian proteins. *J Allergy Clin Immunol*. 2008;121(2):S25.
 6. Mullins RJA. Clinical significance of sensitisation to gelatine colloids in 800 patients. *J Allergy Clin Immunol*. 2008;121(2):S26.
 7. Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, Lewis B, 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. Commins SP, Platts-Mills TAE. Tick bites and red meat allergy. *Curr Opin Allergy Clin Immunol*. 2013;13:354–9. doi:10.1097/ACI.0b013e3283624560.
 9. Hamsten C, Tran TAT, Commins SP, Platts-Mills TAE, van Hage M. Red meat allergy in Sweden: association with tick sensitization and B-negative blood groups. *J Allergy Clin Immunol*. 2013;132(6):1431–4. doi:10.1016/j.jaci.2013.07.050. See comment regarding reference [41].
 10. Wickner PG, Commins S. The first central American cases of delayed meat allergy with galactose-alpha-1,3-galactose positivity clustered among field biologists in Panama. Abstract 736, AAAAI Annual Meeting, San Diego, USA. February 28–March 4, 2014. <https://aaaai.confex.com/aaaai/2014/webprogram/Paper10445.html>.
 - 11.• Mullins RJ, James H, Platts-Mills TAE, Commins S. The relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose. *J Allergy Clin Immunol*. 2012;129:1334–42. doi:10.1016/j.jaci.2012.02.038.
 12. James HR, Commins SP, Kelly LA, Pochan SL, Workman LJ, Mullins, et al. Further evidence for tick bites as a cause of the IgE responses to alphagal that underlie a major increase in delayed anaphylaxis to meat. *J Allergy Clin Immunol*. 2011;127(2):Suppl: AB243.
 - 13.• Kennedy JL, Stallings AP, Platts-Mills TAE, Oliviera WM, Workman L, James HR, et al. Galactose- α -1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children. *Pediatrics*. 2013;131:e1545–52. doi:10.1342/peds.2012.2585.
- Documented the occurrence of mammalian meat allergy following tick bites in children in a tick-endemic area.
14. Australasian Society of Clinical Immunology and Allergy (ASCI): Acute Management of Anaphylaxis Guidelines. www.allergy.org.au/images/stories/pospapers/ASCI_Acute_Management_of_Anaphylaxis_Guidelines_September2013.pdf.

15. Australasian Society of Clinical Immunology and Allergy (ASCI) ASCIA anaphylaxis event record www.allergy.org.au/health-professionals/anaphylaxis-resources/anaphylaxis-event-record.
 16. van Nunen SA, Said MG, Batty G. Use of expanded search criteria in diagnosing mammalian meat allergy provoked by previous tick bites in individuals who do not live where ticks are endemic. Abstract #2602 European Academy of Allergology and Clinical Immunology Congress and World Allergy Organisation, Milan, Italy, 2013. www.eaaci-wao2013.com.
 - 17.●● Pointreau Y, Commins SP, Calais G, Watier H, Platts-Mills TAE. Fatal infusion reactions to cetuximab: role of immunoglobulin E-mediated anaphylaxis. *Allergy*. 2012;30(3):334. doi:10.1200/JCO.2011.38.4701.
- Emphasised the importance of checking for alphagal positivity prior to therapy with cetuximab in those at risk of severe hypersensitivity reactions owing to the presence of pre-existing IgE specific for alphagal. Noted seven fatalities had occurred in France.
- 18.● Schroeder N, Eccles J, Klaffky EJ, Platts-Mills TAE. Cellular infiltrate induced by bites from the tick *Amblyomma americanum* in subjects with or without IgE to galactose-alpha-1,3-galactose (alpha-gal). AAAAI Meeting March, 2014. <https://aaaai.confex.com/aaaai/2014/webprogram/Paper11525.html>.
- Please see comment for reference 28.
19. Australasian Society of Clinical Immunology and Allergy (ASCI): Advanced Acute Management of Anaphylaxis Guidelines. <http://www.allergy.org.au/health-professionals/papers/advanced-acute-management-of-anaphylaxis-guidelines>.
 20. Jacquenet S, Moneret-Vautrin DA, Bihain BE. Mammalian meat-induced anaphylaxis: clinical relevance of antigalactose-alpha-1,3-galactose IgE confirmed by means of skin tests to cetuximab. *J Allergy Clin Immunol*. 2009;124(3):603–5. doi:10.1016/j.jaci.2009.06.014.
 21. Renaudin J, Jacquenet S, Metz-Favre C, Baudoin E, Engel F, de Blay F, et al. Interest of specific IgE measurement for galactose-alpha-1,3-galactose in unexplained urticaria and angioedema, predominantly nocturnal: about 6 cases. *J Allergy Clin Immunol*. 2012;129(2):AB177.
 - 22.● Morisset M, Richard C, Astier C, Jacquenet S, Croizier A, Beaudoin E, et al. Anaphylaxis to pork kidney is related to IgE antibodies to specific IgE for galactose-alpha-1,3-galactose. *Allergy*. 2012;67(5):699–704.
- Documented greater quantities of alphagal in mammalian offal versus mammalian meat. Implications regarding use of mammalian derivatives in food and other products.
- 23.● Morisset M, Richard C, Zanna H, Jacquenet S, Morel-Codreanu F, Jarlot S, et al. Allergy to cow's milk related to IgE antibodies specific for galactose-alpha-1,3-galactose. Abstract #1617 European Academy of Allergology and Clinical Immunology Congress and World Allergy Organisation, Milan, Italy, 2013. www.eaaci-wao2013.com.
- Reported cow's milk allergy occurring in a mammalian meat-allergic patient after another tick bite. Implications regarding role of the prevention of tick bites.*
24. Nunez R, Carballada F, Gonzalez-Quintela A, Gomez-Rial J, Boquete M, Vidal C. Delayed mammalian meat-induced anaphylaxis due to galactose-alpha-1,3-galactose in 5 European patients. *J Allergy Clin Immunol*. 2011;128(5):1122–4. doi:10.1016/j.jaci.2011.07.020.
 - 25.● Caponetto P, Fischer J, Biedermann T. Gelatine-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.
- Reported gelatine in food as an allergen provoking anaphylaxis in mammalian meat-allergic patients and reported a reaction delayed by 10h.*
26. Jappe U. Update on meat allergy: α -Gal: a new epitope, a new entity? *Hautarzt*. 2012;63(4):299–306. doi:10.1007/s00105-011-2266-y.
 27. Michel S, Scherer K, Heijman IAFM, Bircher AJ. Skin prick test and basophil reactivity to cetuximab in patients with IgE to alpha-gal and allergy to red meat. *Allergy*. 2014;69:403–5. doi:10.1111/all.12344.
 - 28.●● Rispens T, Derksen NIL, Commins SP, Platts-Mills TA, Aalberse RC. IgE production to α -gal accompanied by elevated levels of specific IgG1 antibodies and low amounts of IgE to blood group B. *PLoS ONE*. 2013;8(2):e55566. doi:10.1371/journal.pone.0055566.
- Taken together with the findings of Hamsten et al. [18], the histological study by Schroeder et al. [42] and recent work by Commins et al. [49], this provides insight into the possible mechanism of sensitization of the host to alphagal, with alphagal being transmitted to the host by the tick.
- 29.●● 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.
- Direct evidence that alphagal is present in ticks was provided by Hamsten and colleagues when they demonstrated galactose- α -1,3-galactose in the gut of *Ixodes ricinus* and noted the implication that a host would be exposed to alphagal during a bite.
30. Sekiya K, Fukutomi Y, Nakazawa T, Taniguchi M, Akiyama K. Delayed anaphylactic reaction to mammalian meat. *J Invest Allergol Clin Immunol*. 2012;22(6):437–59.
 31. Lee JH, Kim TH, Kim TH, Kim SC. A case of delayed mammalian meat-induced anaphylaxis due to galactose- α -1,3-galactose. (). 2012;64(1):209.

32. Lee JH, Kim JH, Kim TH, Kim SC. Delayed mammalian meat-induced anaphylaxis confirmed by skin test to cetuximab. *J Dermatol*. 2013;40:577–8. doi:[10.1111/1346-8138.12140](https://doi.org/10.1111/1346-8138.12140).
33. van Nunen SA, Mastroianni M, Fulton R, Fernando S, Basten A. Clinical utility of allergen specific-IgE measurement in the diagnosis of mammalian meat/s-induced anaphylaxis. *Intern Med J*. 2011;41 Suppl 4:4–22. doi:[10.1111/j.1445-5994.2011.02570.x](https://doi.org/10.1111/j.1445-5994.2011.02570.x).
34. van Nunen SA, Zaininger A, Clarke LR, Coyle L, Stevenson W, Fernando SL. Severe anaphylaxis provoked by IgE-mediated reactions to food (red meat) in two patients with systemic mastocytosis. *Intern Med J*. 2009; (Suppl. 5):A145.
35. Guglielmone AA, Beati L, Barro-Battesti DM, Labruna MB, Nava S, Venzal JM, et al. Ticks (ixodidae) on humans in South America. *Exp Appl Acarol*. 2006;40(2):83–100.
36. Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, et al. A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada. *J Allergy Clin Immunol*. 2010;125(6):1327–35. doi:[10.1016/j.jaci.2010.03.015](https://doi.org/10.1016/j.jaci.2010.03.015).
37. Platts-Mills TAE, Commins SP. Emerging antigens involved in allergic responses. *Curr Opin Immunol*. 2013;25:769–74. doi:[10.1016/j.coi.2013.09.002](https://doi.org/10.1016/j.coi.2013.09.002).
38. Bogdanovic J, Halsey NA, Wood RA, Hamilton RG. Bovine and porcine gelatin sensitivity in milk and meat-sensitized children. *J Allergy Clin Immunol*. 2009;124(5):1108–10.
39. Kelso JM, Jones RT, Yunginger JW. Anaphylaxis to measles, mumps and rubella vaccine mediated by IgE to gelatin. *J Allergy Clin Immunol*. 1993;91:867.
40. Sakaguchi M, Nakayama T, Inouye S. Food allergy to gelatin in children with systemic immediate-type reactions including anaphylaxis to vaccines. *J Allergy Clin Immunol*. 1996;98:1058.
41. Sakaguchi M, Hori H, Ebihara T, Irie S, Yanagida M, Inouye S. Reactivity of the immunoglobulin E in bovine gelatin-sensitive children to gelatins from various animals. *Immunology*. 1999;96:286–90.
42. World Allergy Organisation: WAO-GLORIA Module 8. Anaphylaxis. www.worldallergy.org/educational_programs/gloria/slides/US/Anaphylaxis.ppt.
43. Australasian Society of Clinical Immunology and Allergy (ASCIA) ASCIA adrenaline auto-injector e training. <https://etraining.allergy.org.au/login>.
44. TiARA (Tick-induced Allergies Research and Awareness) website, Royal North Shore Hospital, Sydney, Australia: Allergies provoked by ticks. <http://www.tiara.org.au>.
45. University of Virginia, Charlottesville, Virginia, USA. Allergy to Meat website. <http://allergytomeat.wordpress.com/>.
46. • 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. doi:[10.1016/j.jaci.2014.01.024](https://doi.org/10.1016/j.jaci.2014.01.024). Please see comment at reference 41.
47. Australasian Society of Clinical Immunology and Allergy (ASCIA): Allergy Education Resources: tick allergy. http://www.allergy.org.au/images/stories/aer/infobulletins/2014/AER_tick_allergy_2014.pdf.
48. European Centre for Disease Prevention and Control (ECDC): Prevention and control of tick-borne disease in Europe. http://ecdc.europa.eu/en/healthtopics/emerging_and_vector-borne_diseases/tick_borne_diseases/public_health_resources/Documents/1006_PPT%20HP.pdf.
49. Centers for Disease Control and Prevention (CDC): Preventing tick bites. http://www.cdc.gov/ticks/avoid_people.html.