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## Tick bites and red meat allergy

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### Abstract

**Purpose of review**—A novel form of anaphylaxis has been described that is due to IgE antibody (Ab) directed against a mammalian oligosaccharide epitope, galactose-alpha-1, 3-galactose (alpha-gal). Ongoing work regarding the cause and distribution of this IgE response is reviewed.

**Recent findings**—Our recent work has identified a novel IgE Ab response that has been associated with two distinct forms of anaphylaxis: immediate-onset anaphylaxis during first exposure to intravenous cetuximab and delayed-onset anaphylaxis 3–6 h after ingestion of mammalian food products (e.g. beef and pork). Further studies strongly suggested that tick bites were a cause, if not the only significant cause, of IgE Ab responses to alpha-gal in the United States and internationally.

**Summary**—Large numbers of patients with IgE Ab to alpha-gal continue to be identified in the USA and globally. Clinicians should be aware of this IgE response as the reactions often appear to be idiopathic because of the significant delay between eating mammalian meat and the appearance of symptoms.

### Keywords

alpha-gal; anaphylaxis; food allergy; IgE; mammalian meat; tick bites

## INTRODUCTION

Ticks, or Ixodida, are an order of obligate bloodsucking parasites within the class Arachnida. This class includes many species that can cause immunological sensitization (Fig. 1). The ticks have been recognized as a source of infection for over 100 years, and a long list of viral, bacterial, and rickettsial diseases are primarily spread by ticks. Tick saliva contains many different proteins with antihemostatic, anti-inflammatory, anesthetic, and

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### Conflicts of interest

S.P.C. and T.A.E.P.-M. report ongoing support for IgE assays from Thermo Fisher. T.A.E.P.M. has a patent for the use of IgE assays to identify the risk of anaphylaxis with recombinant molecules. He is also a consultant to Viracor-IBT Laboratories.

immunomodulatory properties, which collectively help the tick to prolong the attachment and feed successfully [1]. The host organisms make immune responses to tick saliva, and these responses play a role in reducing the tick attachment and also reducing the infection [2]. The importance of tick saliva is reflected in the rapid evolution of proteins in their saliva [3,4]. However, the evolution of ticks that feed on mammals has occurred primarily, if not exclusively, with nonprimate mammals as the primary host [5]. It could, of course, be argued that the ability to remove ticks and other parasites from our skin is one of the advantages of hands with opposable thumbs. In addition, it is likely that the immune response to ticks feeding on humans reflects the fact that we are an accidental or irrelevant host.

## TICKS AND IgE ANTIBODY RESPONSES

Some species of ticks can cause anaphylactic reactions during the bite. There have been multiple reports from Australia and Europe, but surprisingly only one case report from the United States. These reactions have been shown to be related to IgE antibodies to salivary proteins. Interestingly, a report from Denmark demonstrated that a plant used to treat allergic reactions caused by tick bites in northern Afghanistan was indeed an active antihistamine [6\*].

Prior to 2008, three observations had been made that appeared unrelated, but were ultimately related to our story. First, the allergic disease group at the Karolinska Institute in Sweden recognized that some patients who presented with positive skin tests to cat allergens had IgE antibodies specific for an oligosaccharide on cat IgA [7]. Second, two allergists in practice had independently reported to their local societies about patients who developed allergy to meat after being bitten by ticks [8\*]. Third, the monoclonal antibody cetuximab, which is produced in a mouse cell line, SP2/0, was reported to give rise to hypersensitivity reactions in up to 20% of patients treated with this monoclonal in Tennessee or North Carolina [9]. Working out the specificity of the IgE antibodies giving rise to cetuximab reactions became possible because pretreatment sera were available in Tennessee, Qinwei Zhou and his colleagues at ImClone defined the glycosylation of cetuximab, and ImClone provided the monoclonal antibody expressed in a different cell line (CHO) [10,11]. Using an assay for cetuximab with the mAb bound to an ImmunoCAP, it became possible to prove that reactions were 'caused by' preexisting IgE antibodies to the oligosaccharide on the Fab portion of this molecule [10,12\*]. This oligosaccharide, galactose- $\alpha$ -1,3-galactose ( $\alpha$ -gal) is a blood group substance of the nonprimate mammals, and therefore would not be part of the immune response to tick saliva in their normal hosts. The finding of IgE antibodies to  $\alpha$ -gal in up to 20% of patients (and controls) in Tennessee, Virginia, North Carolina, Arkansas, and southern Missouri led to two questions: why were these antibodies so common in this area, and were they associated with any other diseases?

After the  $\alpha$ -gal epitope had been defined, it was quickly made clear that the previously recognized oligosaccharide epitope on cat IgA was  $\alpha$ -gal [13]. Although a relationship between mammalian meat allergy and tick bites had been suggested in Australia [8\*], the tick connection was not immediately obvious in the United States or Sweden. After excluding many possible causes, including helminth and fungal infections, the closest match

for the distribution of these antibodies was the highest prevalence of Rocky Mountain spotted fever (RMSF). This led to a detailed analysis of histories of tick bites and serological assays using *Amblyomma americanum* and *Dermacentor variabilis* extracts [14<sup>11</sup>]. In addition, it was possible to monitor the rise in IgE antibodies to alpha-gal after tick bites (Fig. 2). Taken together, the results provided strong evidence that tick bites were an important, if not the only, cause of these antibodies in the United States [14<sup>11</sup>]. More recently, van Hage and her colleagues in Stockholm have reported clear evidence that the alpha-gal epitope is present in the gut of *Ixodes ricinus* [15<sup>12</sup>]. Strikingly, the evidence was that the tick bites that gave rise to this response were characterized by persistent itching at the site of the bite [14<sup>11</sup>]. By contrast, pruritic responses to tick bites in an area endemic for Lyme disease were found to be negatively associated with serological responses to *Borrelia burgdorferi* [16].

Only very limited data are available about the cellular response in the skin following bites of different ticks. The fact that the responses to *A. americanum* are so persistent and so profoundly pruritic suggests that a significant immune response is occurring at the site of the bite [17]. A recent report of multiple pruritic papules caused by *Haemaphysalis longicornis* in Korea demonstrated abundant eosinophils at the sites of the bites [18]. However, the staining technique they used would probably not identify basophils. On the other hand, a recent study [19] of immune responses to *Ixodes scapularis* saliva emphasized the role of neutrophils in preventing *Borrelia* infection.

Studies on the antibody response to *A. americanum* tick bites have examined both the specificity of the antibodies and the isotypes involved. Using NMR, it has been confirmed that the antibodies are primarily directed at the two terminal galactoses [20]. It is important to remember that all immuno-competent humans (as well as Old World monkeys and apes) have circulating IgG antibodies to alpha-gal [21]. These antibodies are predominantly IgG2 and are thought to be induced by continuous antigenic stimulation by oligosaccharide antigens on bacteria in the gut [21]. Independent measurements in Virginia and Amsterdam do not support the earlier evidence that the IgG antibodies to alpha-gal are equal to 1% of circulating IgG. Our results suggest that these antibodies are around 1 µg/ml (i.e. 0.1%). Following tick bites, the IgG antibodies increase in parallel with IgE antibodies, but they are predominantly IgG1 [22<sup>13</sup>]. One interesting question is whether the 'natural' IgG2 antibody response influences the immune response to the same epitope induced by tick bites. In addition, the resulting antibody response (IgG2 vs. IgE) likely reflects the route of sensitization (intestinal vs. skin) and predicts the clinical outcome (tolerance vs. allergy), which may establish a model for understanding the mechanisms controlling the immune responses leading to oral tolerance on the one hand or food allergy on the other.

## EPIDEMIOLOGY OF THE IgE ANTIBODY RESPONSE TO ALPHA-GAL AND THE ASSOCIATED REACTIONS TO RED MEAT

Using the assay for IgE Ab to alpha-gal, we screened sera from different groups of patients who had presented to the allergy clinic. It rapidly became clear that there was a group of patients who consistently reported urticarial or anaphylactic reactions occurring 3–5 h after eating red meat [23]. In keeping with the known distribution of the oligo-saccharide, these

patients also had positive skin tests and serum assays to beef, pork, and lamb, as well as milk, cat, and dog [24].

Over the 4 years since we first described delayed urticarial or anaphylactic reactions to red meat, we have become aware of over 1000 cases in which the history has been confirmed by a serum assay for IgE antibodies to alpha-gal. However, these cases include a mixture of de-identified case reports from other physicians, cases enrolled in our own clinics, and series of cases enrolled by other physicians. We have good evidence that these cases are common in the original southeastern states but also extending into the midwest states where the same ticks are prevalent (e.g. Oklahoma). In addition, we have knowledge of a few cases in surrounding states and also as far north as Nantucket. There also exist 'hot spots' in different areas of these states where the landscape is unique or different (e.g. East Hampton portion of Long Island, New York). However, there was initially major bias in certain locales because of enthusiasm and increased awareness of the condition. Thus, it is not yet possible to connect that data into an estimate of overall prevalence, which is a goal of future studies.

## **LATE-ONSET AND DELAYED REACTIONS TO MAMMALIAN FOOD PRODUCTS OUTSIDE THE USA**

We are now aware of the physicians who have identified cases of delayed anaphylaxis in Australia, France, Germany, Sweden, Spain, Japan, and Korea. Notably, in each of these countries, there is evidence that tick bites are the primary cause of the sensitization and that the primary or sole sensitization is to alpha-gal.

### **Australia**

Following Dr Van Nunen's [8<sup>\*</sup>] original observations in Sydney, we established collaboration with Dr Mullins who works in Canberra, which is within the same region. We have now assayed more than 50 sera from that region, and there is no doubt that IgE to alpha-gal is present and associated with food reactions to mammals, including kangaroo meat [25<sup>\*</sup>].

### **Germany**

Dr Jappe has been aware of the reactions to cetuximab as well as allergic reactions to beef. Her lab at the Borstel Institute near Hamburg has shown IgE binding to cetuximab by western blot and, subsequently, that those results correlated well to immunoassay results for IgE to alpha-gal using biotinylated reagents [26].

### **France**

Dr Moneret-Vautrin and her group in Nancy identified three cases in 2009 and reported on skin testing [27]. More recently, they have extended their work to study other foods including goat, horse, and particularly pork and beef kidneys as a cause of severe delayed reactions in patients with IgE to alpha-gal [28<sup>\*\*</sup>].

## Sweden

Dr Van Hage and her colleagues originally reported that some IgE antibodies binding to cat extracts were specific for an oligosaccharide on cat IgA and went on to show that the oligosaccharide on cat IgA was alpha-gal [13,29]. More recently, they have used antibodies against alpha-gal in human sera to stain the cryostat preparations of the tick which is thought to induce these responses in Stockholm [15<sup>\*\*\*</sup>]. The area of Sweden where we have screened sera from school children is almost 800 miles north of Stockholm and less than 1% of those sera tested positive for IgE to alpha-gal [30,31<sup>\*</sup>]. Interestingly, there are no ticks in that area.

## Japan

Dr Sekiya and colleagues in Sagamihara reported the case of a 74-year-old woman with no history of atopy or allergic disorders who reported anaphylaxis 5 h after eating roast beef [32]. The patient reported being bitten by ticks 2 months before the reaction. The authors performed an open challenge with 50 g of roast pork and the patient developed generalized urticaria with swelling and redness of the face 5 h after consuming the pork. An open challenge with 50 g of roast chicken produced no symptoms.

## Korea

A group in Seoul led by Dr Kim has reported the case of a 67-year-old man who experienced anaphylaxis 7 h after eating mammalian meat. In addition, the patient reported recurrent episodes of delayed urticaria several hours after consuming pork, beef, or lamb. He denied any reactions to milk, fish, and poultry. The authors performed intradermal testing with cetuximab at concentrations of 5, 50, and 500 µg, which showed positive responses at each concentration, and that the response was larger with increasing concentration.

## Africa

In Africa, although IgE to alpha-gal has been identified in both adults and children, those reports do not include evidence of reactions to mammalian meat [31<sup>\*</sup>,33].

## IgE ANTIBODIES TO GALACTOSE ALPHA-1,3-GALACTOSE IN CHILDREN

All reported cases of hypersensitivity reactions to cetuximab have been in adults, in keeping with the use of this monoclonal Ab to treat colon cancer and head and neck cancer [34]. In addition, the original cases of delayed anaphylaxis to red meat were all in adults [23]. We assumed at that time that children were not bitten by ticks as much as adults; however, we already knew that IgE Ab to alpha-gal was common among children in an African village and in rural Ecuador [31<sup>\*</sup>,35]. In addition, we have heard reports about children having multiple tick bites at camps in Tennessee. Over the last 3 years, particularly with the screening in Lynchburg, we have identified a series of children who presented with either anaphylaxis, recurrent acute episodes of urticaria, or chronic urticaria [36<sup>\*\*\*</sup>]. The serology of these cases appears to be similar to that of the adults, as does the severity of the reactions: 44% had anaphylaxis at presentation and 46% sought care in an emergency department/urgent care center [36<sup>\*\*\*</sup>]. At this time, however, we have no local reference base to estimate the prevalence of IgE Ab to alpha-gal in children. It would be difficult to ascertain an accurate estimate without surveying a large population of children to identify the prevalence

of the IgE antibodies. For the moment, we have chosen not to carry out challenges on children because we believe that the mechanism of the delay can best be studied in adults.

## CONCLUSION

The discovery of IgE antibodies to the oligosaccharide alpha-gal has made it possible to investigate several novel aspects of allergic disease. The obvious thing is that the glycosylation of therapeutic recombinant molecules, particularly monoclonal antibodies, can create a risk for severe hypersensitivity reactions [24]. The IgE responses induced by tick bites give rise to multiple questions. It is clear that these responses can occur in individuals of all ages and do not appear to be different in individuals who are otherwise atopic. In some cases, the IgE responses are very high in titer and make a large contribution to total serum IgE. The possible mechanisms for these responses include direct switch of B cells from B $\mu$  to B $\epsilon$  occurring outside an organized germinal center, priming of B cells in the skin, and questions about the relevance of T cells to the response. It is clear that understanding how tick bites induce such dramatic IgE responses could have great significance to IgE responses in general and to the significance of the skin in particular. In addition, because these IgE antibodies also bind to a wide range of mammalian proteins we recognized the syndrome of 'delayed anaphylaxis to mammalian meat' [23]. However, the most interesting feature of the clinical reactions may be that the first symptoms (i.e. itching or urticaria) occur 3–6 h after eating meat and would normally be regarded as 'spontaneous' or 'idiopathic' anaphylaxis. Understanding the factors that control the delay may provide real insight into the factors that control anaphylaxis.

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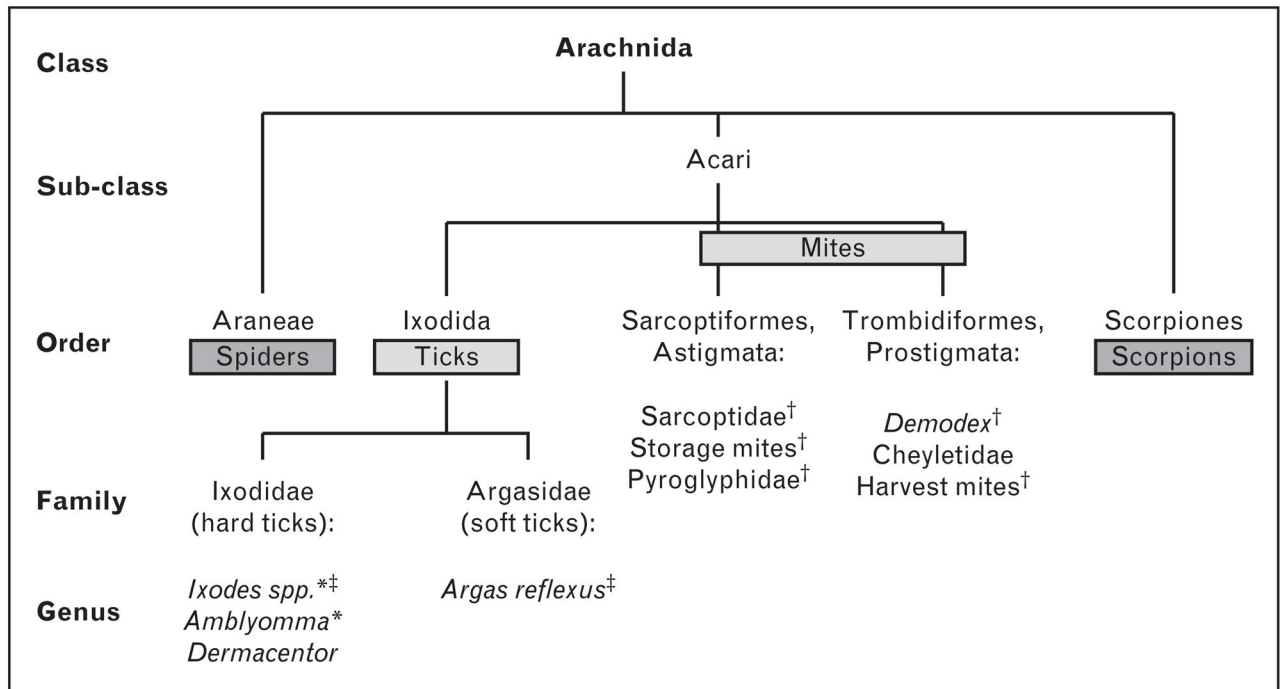
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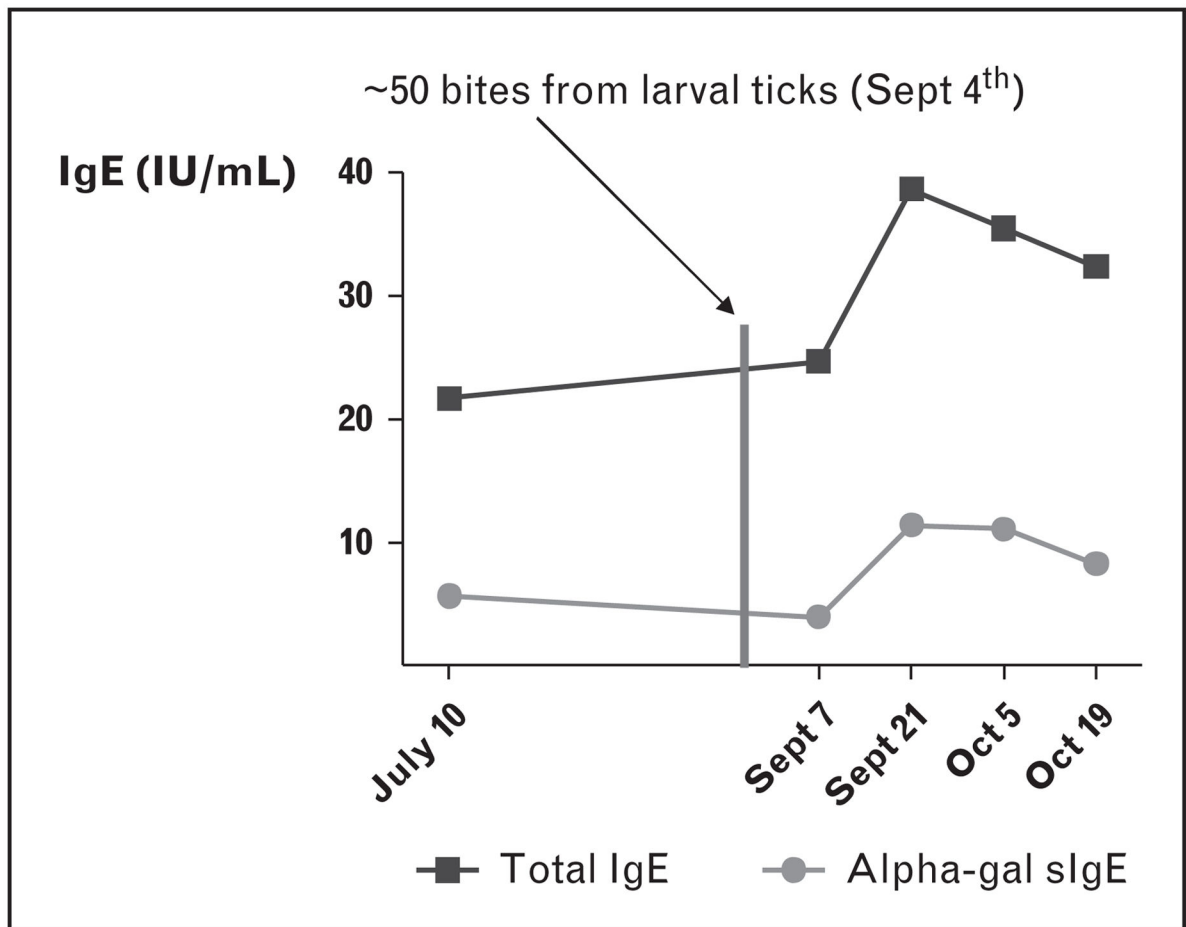
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**KEY POINTS**

- Tick bites are an important cause of IgE antibody responses, including IgE responses to tick proteins and to the oligosaccharide galactose-alpha-1,3-galactose.
- Many patients who have IgE antibodies to alpha-gal experience delayed anaphylactic and urticarial reactions after eating mammalian meat, which carries the oligosaccharide.
- The association between tick bites, IgE antibodies to alpha-gal, and delayed reactions to red meat has now been reported from multiple countries, including Australia, Sweden, France, Spain, and Japan, as well as the United States.

**FIGURE 1.**

Classification of the Arachnida, a class within the phylum Arthropoda. <sup>†</sup>Known to cause sensitization unrelated to alpha-gal. <sup>\*</sup>*Amblyomma americanum*, *Ixodes ricinus*, and *Ixodes holocyclus* have been reported to induce IgE to alpha-gal. <sup>‡</sup>*Ixodes holocyclus* and *Argas reflexus* have been associated with anaphylaxis at the time of a tick bite.



**FIGURE 2.**

Change in total IgE and alpha-gal-specific IgE over the weeks following approximately 50 bites from larval ticks in a patient.