

2016 Alpha-Gal Citizen's Petition

Task Force on Alpha-Gal
Documents by Reference Number

Ref #	Reference Notation
01	Wagner, K.D., Bell, M.C., Pesek R.D., and Kennedy, J.L., Fifty-six-year-old man with anaphylaxis: A novel delayed food hypersensitivity reaction, The Journal of the Arkansas Medical Society, November 2015.
02	State of Arkansas, 90 th General Assembly, Act 1247 of the 2015 Regular Session
03, 05 07, 15	Van Nunen, S., Galactose-Alpha-1, 3-Galactose, Mammalian Meat and Anaphylaxis: A World-Wide Phenomenon, Current Treatment Options in Allergy, (2014). 1:262-277, DOI 10.1007/s40521-014-0022-0
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Fifty-six-year-old man with anaphylaxis: A novel delayed food hypersensitivity reaction

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KEY WORDS: Meat Allergy, Tick Exposure, Delayed anaphylaxis, Urticaria, Angioedema

ABSTRACT

Anaphylaxis and urticaria are commonly seen in both primary care and allergy clinics. Foods, drugs, and insects are frequent culprits for immediate reactions; however, the trigger for recurring and/or chronic episodes is often unclear. We present a 56-year-old male with recurrent symptoms of urticaria, angioedema, and anaphylaxis found to be triggered by sensitization to galactose-alpha 1, 3-galactose (alpha-gal), a novel food allergen.

CASE PRESENTATION CHIEF COMPLAINT:

Urticaria and angioedema

HISTORY OF PRESENT ILLNESS:

A 56-year old male with history of occasional urticaria presented to the University of Arkansas for Medical Sciences (UAMS) emergency department (ED) following an episode of anaphylaxis. He reported the onset of diffuse urticaria that woke him from sleep. The patient took 25 mg of diphenhydramine and 10 mg of cetirizine; however, the hives continued to progress. Additionally, he developed abdominal discomfort and the sudden urge to defecate. He became lightheaded and called for his wife before losing consciousness. She administered an Epi-Pen injection and called 911. Upon arrival of emergency personnel, the patient had regained consciousness, but his blood pressure was 74/54. He was given a normal saline bolus in route to the ED.

PHYSICAL EXAM:

Upon arrival to the ED, the patient's blood pressure had normalized, and his physical exam was

notable for a rash (**Figure 1**) as well as slight (1+) edema of the hands. There was no facial or tongue swelling and no stridor or wheezing. He was given diphenhydramine 50 mg, methylprednisolone 125 mg, and famotidine 40 mg.

HOSPITAL COURSE:

After stabilization in the ED, further history revealed a similar event including hives, angioedema, and syncope that occurred 3 years previously. At that time, the patient was taking an angiotensin-converting enzyme (ACE)-inhibitor for hypertension, which was discontinued due to concerns that the medication had triggered the event. Daily cetirizine was prescribed due to concerns of chronic urticaria and angioedema; however, it was stopped a few months later because no further anaphylactic episodes occurred. After stopping cetirizine, the patient developed recurrent episodes of hives without angioedema, syncope, or other symptom. He also noted an increase in the frequency and severity of hives during the two weeks prior to the presentation above. The patient recalled no new foods, medications, or stings prior to these events. However, the patient did consume pork the evening preceding the described presentation. Additionally, he reported spending a considerable amount of time outdoors and had received several tick bites leading up to the current event. A serum tryptase level was drawn at the time of presentation and was elevated at 16.3 mg/L (reference 0-11mg/L), consistent with anaphylaxis. The patient was observed overnight with resolution of his symptoms.

POST-HOSPITAL COURSE

Upon discharge, the patient was seen in the UAMS Allergy and Immunology Clinic. Follow-up testing revealed normalization of serum tryptase to 4 mg/L, a

slightly elevated serum total IgE level of 220 IU/L (reference 2-214 IU/L), and an elevated serum specific-IgE to the disaccharide Galactose-alpha 1,3-Galactose of 45.60 IU/L (reference <0.35 IU/L). Other laboratory is listed in Table I.

QUESTION #1: WHAT IS GALACTOSE-ALPHA 1,3-GALACTOSE (ALPHA-GAL)?

Galactose-Alpha 1,3-Galactose (alpha-gal) is a disaccharide found as a terminal sugar on glycosylated cell surfaces of bacteria, most animals, and lower primates.¹ Humans lack the gene encoding the enzyme galactosyltransferase and thus do not express alpha-gal on their cell membranes.¹ The absence of this disaccharide plays a beneficial role in protecting humans from many enveloped viruses that utilize this sugar as a receptor for cell entry.² In fact, all immunocompetent humans will have IgG antibodies to the disaccharide alpha-gal, but only a subgroup of patients in the United States has IgE class antibodies to alpha-gal.³

QUESTION #2: WHAT IS THE CONNECTION BETWEEN ALPHA-GAL AND ALLERGY?

A link between alpha-gal and cetuximab, a chimeric mouse-human IgG1 monoclonal antibody



Figure 1: Right leg of the case patient with urticaria preceding the anaphylactic event described in the manuscript.

Table I: Laboratory evaluation in allergy clinic.

CBC with Differential	Patient Values	Normal Range
WBC	10.76 k/UL	4.0 – 11.0 k/ μ L
Neutrophils Percent	53.7 %	47.0 – 82.0 %
Lymphocytes Percent	34.2 %	15.0 – 45.0 %
Monocytes Percent	10.1 %	2.0 – 12.0 %
Eosinophils Percent	1.5%	0.0 – 6.0 %
Basophils Percent	0.5 %	0.0 – 2.0 %
Neutrophils Absolute Count	5.78 k/UL	150 – 450 k/ μ L
Lymphocytes Absolute Count	3.68 k/UL	1.00 – 5.00 k/ μ L
Monocytes Absolute Count	1.09 k/UL	0.00 – 1.00 k/ μ L
Eosinophils Absolute Count	0.16 k/UL	0.00 – 0.60 k/ μ L
Basophils Absolute Count	0.05 k/UL	0.00 – 0.20 k/ μ L
Thyroid Studies	Patient Values	Normal Range
TSH	2.060 mIU/mL	0.47-4.68 mIU/mL
FT4	1.24 ng/dL	0.65-1.85ng/dL
Allergy Evaluation	Patient Values	Normal Range
Tryptase (in ED)	16.3mg/L	0-11mg/L
Tryptase (in clinic)	4mg/L	0-11mg/L
IgE	220 IU/L	2-214 IU/L
IgE to alpha-gal	45.6 IU/L	<0.35 IU/L
WBC= white blood count; TSH= thyroid stimulating hormone; FT4= free T4; IgE= immunoglobulin E		

against epidermal growth factor used in chemotherapeutic treatment regimens of various cancers, was established after it was noted that a subset of patients had anaphylaxis on **first exposure** to this medication.⁴ Allergic reactions usually require an initial exposure (sensitization) to an antigen leading to the production of the allergic antibody, IgE, by B cells and plasma cells. IgE created during the sensitization step moves through the circulation until it binds the surface of mast cells. With re-exposure to the same antigen, there is degranulation of mast cells and basophils, leading to clinical symptoms of anaphylaxis (**Figure 2**). However, the allergy to cetuximab is different, as patients who developed anaphylaxis had never before been exposed to the drug. Interestingly, one of the first cases was described in Arkansas and further investigation revealed that patients in the southeastern United States had a much higher incidence of serum-specific IgE and anaphylaxis to cetuximab.³ After careful analysis of the potential allergens on cetuximab, it was determined that during production, alpha-gal was placed on the surface of the antibody, and it was IgE to this carbohydrate moiety that subsequently led to anaphylaxis.⁴

Often overlooked in the cetuximab manuscript is a group of 6 subjects among the control cohort who

had recurrent anaphylaxis unrelated to this medication. Each of these subjects also had IgE to cetuximab, alpha-gal, and beef with no previous exposure to cetuximab.⁴ In 2009, researchers at the University of Virginia, described 24 individuals that developed anaphylaxis **3-6 hours** after eating red meat, an unusually long time for most IgE-mediated food reactions. The individuals also had serum IgE specific to cetuximab and alpha-gal.⁵ The authors concluded that these patients had **delayed** food hypersensitivity to alpha-gal induced by ingestion of mammalian meat, including beef, pork, and lamb. The geographical distribution of patients in this study correlated with the locations of those with increased risk of cetuximab hypersensitivity reactions, including Virginia, North Carolina, Tennessee, Arkansas, and Missouri.⁵ Interestingly, many patients identified had previously tolerated red meat without incident, suggesting a new exposure resulted in the production of IgE to alpha-gal. Researchers from several universities suspected regionally important triggers such as inhalant and fungal allergens, as well as helminthes, but no correlation could be found. It was noted that the distribution of hypersensitivity to cetuximab and red meat correlated with areas where Rocky Mountain Spotted Fever (RMSF) and human Ehrlichiosis are endemic.^{6,7}

QUESTION #3: WHAT IS THE CONNECTION BETWEEN TICK EXPOSURE AND ALPHA-GAL ALLERGY?

Both RMSF and human Ehrlichiosis are arthropod-borne diseases most notably distributed by the lone star tick (*Amblyomma americanum*). The lone star tick occupies an area that extends across the south-central and southeastern United States and is expanding.^{7,8} lone star tick bites can induce an increase in both total serum IgE and serum-specific IgE to alpha-gal.⁹ Furthermore, sera from 125 individuals living in Virginia demonstrate a positive correlation between serum-specific IgE to alpha-gal and proteins from emulsified Lone star tick bodies.⁶

QUESTION #4: DOES THIS ALLERGY OCCUR IN CHILDREN?

Although first described in adults, in 2013 Kennedy *et al.* described 45 pediatric patients with anaphylaxis and urticaria 3-6 hours after eating mammalian meat. These patients demonstrated high levels of alpha-gal IgE and IgE for beef (r=0.89) and pork (r=0.87). Furthermore, the geographical distribution of children in this study mirrored that of the adult populations with the majority of patients located in the southeastern United States where the Lone star tick is endemic. Greater than 90% of children with positive IgE to alpha-gal reported tick bites in the previous

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SENSITIZATION STAGE

① Antigen (allergen) exposure

② Plasma cells produce IgE antibodies against the allergen

③ IgE antibodies attach to mast cells and basophils

ANAPHYLAXIS STAGE

④ Re-exposure to allergen

⑤ Allergen combines with IgE attached to mast cells and basophils, which leads to degranulation and release of histamine and other chemical mediators

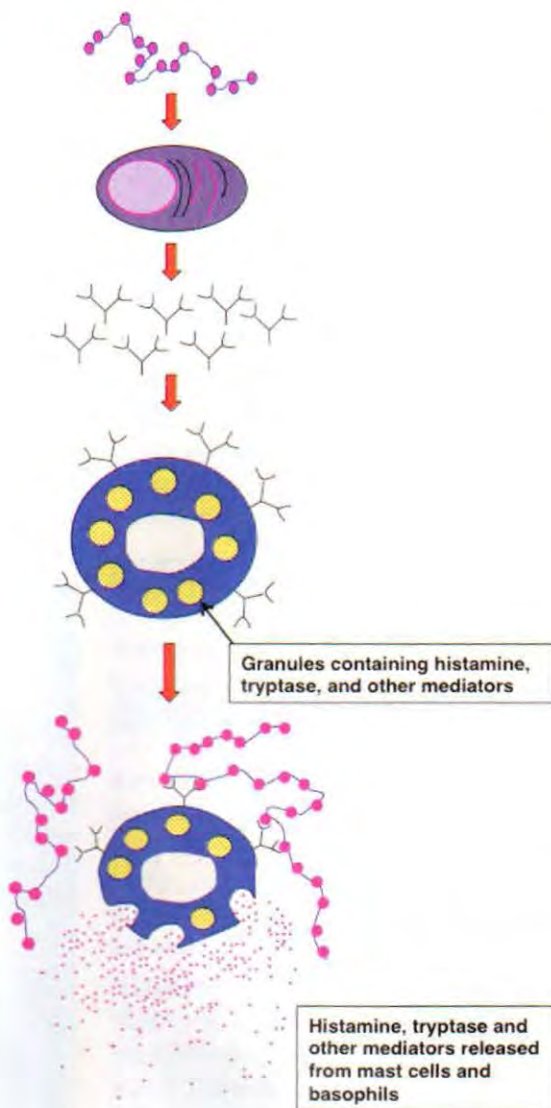


Figure 2: Typical IgE-mediated reactions. See manuscript for details regarding this figure.

year, and many reported persistent itching, swelling, and erythema around the area of the tick bite lasting for 2 to 3 weeks, a more prolonged course than patients without an IgE response to alpha-gal.¹⁰

QUESTION #5: WHAT SHOULD I TELL MY PATIENT WITH ALPHA-GAL ALLERGY?

Patients who have allergy to alpha-gal should meticulously avoid all mammalian meat products. It is important to note that if a patient is tolerating mammalian dairy products these items do not have to be stopped. Patients with IgE to alpha-gal and a clinical history suggestive of this disease should be provided with an epinephrine auto injector. Lastly, it is the experience of the authors that tick avoidance will lead to waning of the IgE antibodies to alpha-gal over time, and it may be possible to reintroduce mammalian meat. However, reintroduction of mammalian meats

should only be performed in a controlled setting under the supervision of a clinician experienced in the treatment of anaphylaxis.^{6,10}

CONCLUSIONS

Our patient presented with delayed hypersensitivity following mammalian meat ingestion with elevated serum-specific IgE to alpha-gal. He has successfully avoided mammalian meat, and he has had no further episodes of anaphylaxis. This case represents a novel food allergy with delayed anaphylaxis to an oral carbohydrate allergen. It can affect adults and children and has a higher prevalence in south-central and southeastern United States. The disease prevalence correlates with the distribution of the habitat of the lone star tick (*A. americanum*), though the evidence for causation remains to be seen. Physicians in Arkansas should consider this diagnosis in patients

who present without an immediate trigger for recurrent episodes of urticaria and/or anaphylaxis and have a clinical history supporting the diagnosis.

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PubMed

Abstract

J Ark Med Soc. 2015 Nov;112(7):110-2.

Fifty-six-year-old man with anaphylaxis: A novel delayed food hypersensitivity reaction.

Wagner KD, Bell MC, Pesek RD, Kennedy JL.

Abstract

Anaphylaxis and urticaria are commonly seen in both primary care and allergy clinics. Foods, drugs, and insects are frequent culprits for immediate reactions; however, the trigger for recurring and/or chronic episodes is often unclear. We present a 56-year-old male with recurrent symptoms of urticaria, angioedema, and anaphylaxis found to be triggered by sensitization to galactose-alpha 1, 3-galactose (alpha-gal), a novel food allergen.

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1 State of Arkansas
2 90th General Assembly
3 Regular Session, 2015
4

As Engrossed: H3/11/15
A Bill

HOUSE BILL 1658

5 By: Representatives J. Mayberry, Tosh
6

7 **For An Act To Be Entitled**

8 AN ACT TO CREATE THE TASK FORCE ON ALPHA-GAL; AND FOR
9 OTHER PURPOSES.

10
11
12 **Subtitle**

13 TO CREATE THE TASK FORCE ON ALPHA-GAL.
14
15

16 BE IT ENACTED BY THE GENERAL ASSEMBLY OF THE STATE OF ARKANSAS:
17

18 SECTION 1. Arkansas Code Title 20, Chapter 15, is amended to add an
19 additional subchapter to read as follows:

20 Subchapter 20 – Task Force on Alpha-gal

21
22 20-15-2001. Findings – Purpose.

23 (a) The General Assembly finds:

24 (1) Alpha-gal allergies are a reaction to galactose-alpha-1, 3-
25 galactose, where the body is overloaded with immunoglobulin E antibodies on
26 contact with the galactose carbohydrate;

27 (2) Bites from the lone star tick, which transfer this
28 carbohydrate to the victim, have been implicated in the development of this
29 delayed allergic response which is triggered by the consumption of mammalian
30 meat products;

31 (3) Alpha-gal allergies most often occur in the central and
32 southern states such as Arkansas, where the lone star tick is more prevalent;

33 (4) A typical allergic reaction to Alpha-gal has a delayed
34 onset, occurring four to eight (4-8) hours after the consumption of mammalian
35 meat products, instead of the typical rapid onset with most food allergies;

36 (5) Since the reaction to eating mammal meat is delayed by



1 several hours, the proper diagnosis is often missed or misdiagnosed;

2 (6) People who are affected by Alpha-gal have to be constantly
3 vigilant about the ingredients they consume, because an allergic reaction can
4 be severe and life-threatening; and

5 (7) As doctors are not required to report the number of patients
6 suffering with Alpha-gal, the true number of affected individuals is unknown.

7 (b) The purpose of this subchapter is to promote awareness and
8 encourage efforts to treat Alpha-gal in the state.

9
10 20-15-2002. Task Force on Alpha-gal – Creation.

11 (a) The Task Force on Alpha-gal is created.

12 (b) The task force shall be composed of the following *sixteen (16)*
13 members:

14 (1) One (1) senator appointed by the President Pro Tempore of
15 the Senate;

16 (2) Two (2) members of the House of Representatives appointed by
17 the Speaker of the House of Representatives;

18 (3) The Director of the Department of Health or his or her
19 designee, serving as an ex-officio, nonvoting member;

20 (4) The Insurance Commissioner or his or her designee, serving
21 as an ex-officio, nonvoting member;

22 (5) The Secretary of the Arkansas Agriculture Department or his
23 or her designee, serving as an ex-officio, nonvoting member;

24 (6) Three (3) members who are employed by the Department of
25 Health and designated by the Director of the Department of Health;

26 (7) One (1) member who is designated by the Arkansas Hospitality
27 Association;

28 (8) One (1) member who is designated by the Arkansas State Board
29 of Nursing;

30 (9) One (1) member who is designated by the Arkansas Pharmacist
31 Association;

32 (10) One (1) member who is designated by the American Academy of
33 Allergy, Asthma, and Immunology;

34 (11) One (1) member who is designated by the American College of
35 Allergy, Asthma, and Immunology; and

36 (12) Two (2) members who are designated by the Division of

1 Agriculture of the University of Arkansas.

2 (c) The terms of the legislative members of the task force shall
3 expire on December 31, 2016.

4 (d) Nonlegislative members shall serve at the pleasure of the
5 organizations they represent.

6 (e) Vacancies on the task force shall be filled in the same manner as
7 provided for the initial appointment.

8 (f) The chair shall be one (1) of the legislative members of the task
9 force and shall be selected by the legislative members of the task force.

10 (g) The task force shall meet as often as is deemed necessary by the
11 chair.

12 (h) The chair shall call the first meeting, which shall be held no
13 later than sixty (60) days after July 31, 2015.

14 (i) The members of the task force shall serve without compensation and
15 shall not receive per diem, mileage, or stipends.

16 (j) The task force shall receive staff support from the Bureau of
17 Legislative Research.

18
19 20-15-2003. Task Force on Alpha-gal – Duties.

20 (a) The Task Force on Alpha-gal shall make recommendations designed to
21 improve and increase knowledge and treatment throughout the state for alpha-
22 gal, especially for emergency room healthcare professionals.

23 (b) The task force shall submit a report to the Legislative Council,
24 the Senate Committee on Public Health, Welfare, and Labor, and the House
25 Committee on Public Health, Welfare, and Labor no later than October 1, 2016.

26
27 */s/J. Mayberry*

28
29
30 **APPROVED: 04/08/2015**

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

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Keywords Mammalian meat · Anaphylaxis · Alphagal · Gelatine allergy · Tick-induced allergies · Mastocytosis · Cetuximab

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

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.

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ALPHA-GAL (MAMMALIAN MEAT) ALLERGY: IMPLICATIONS FOR PHARMACISTS

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What Is Alpha-gal and Mammalian Meat Allergy?

Alpha-gal (galactose-alpha-1,3-galactose), a mammalian oligosaccharide, has recently been implicated in delayed anaphylaxis reactions to mammalian meat. First described in 2009, the alpha-gal allergy (red meat or mammalian allergy) is a novel form of IgE-mediated anaphylaxis; unlike most anaphylaxis, this reaction is delayed. Individuals with high IgE titers to alpha-gal have experienced urticaria, angioedema, and anaphylaxis symptoms **3 TO 6 HOURS** after ingesting mammalian meat (beef, pork, lamb, venison, goat, and bison), which is rich in alpha-gal.¹

Many animal by-products may contain the alpha-gal epitope. Animal by-products derived from turkey, chicken, and fish, however, do not.² Whereas the alpha-gal epitope is also present in cat IgA, a monoclonal antibody found in cat dander, cat exposure has not been associated with allergic reactions. However, patients with the alpha-gal allergy have shown positive skin and blood tests to cat IgA.¹

The alpha-gal allergy affects both children and adults.³ The severity of the allergy and the allergy itself may recede over time.¹

Evolution of Alpha-gal

Humans do not naturally produce alpha-gal epitopes, as the alpha-1,3-glycosyltransferase enzyme is inactivated in humans, old world monkeys, and apes. Other mammals, like new world monkeys, placental mammals, marsupials, and prosimians, however, produce alpha-gal and the enzyme. Humans produce IgG2 anti-gal naturally, which protects them against normal bacteria flora in the gut that produces the alpha-gal epitope.⁴ Patients with blood group B or AB have fewer anti-gal antibodies and therefore may be less likely to develop the mammalian meat allergy (or develop a milder reaction).⁵ Research suggests that exposure to the alpha-gal epitope in a tick bite may cause normal anti-gal antibody formation to switch from IgG2 to the IgE involved in the delayed anaphylaxis response to the specific types of mammalian meat previously mentioned.^{5,6}

Prevalence and Location

Experts estimates that thousands of Americans have the alpha-gal allergy,⁷ with a causal relationship between lone star tick bites and these anaphylactic reactions. Individuals bitten by lone star ticks can develop IgE antibodies to alpha-gal. The highest infestations of lone star ticks occur in the eastern states.⁸

Pharmacist's Role

To prevent anaphylaxis, affected patients should avoid any medication, supplements, foods, etc that may contain the alpha-gal epitope; this is their only treatment option. A comprehensive list of medications containing alpha-gal or animal by-products is unavailable at this time. Alpha-gal allergy testing is commercially available and requires a serum sample.

As previously mentioned, many animal by-products may contain the alpha-gal epitope. Gelatin, derived from beef, is one.⁹ Animal-derived magnesium stearate is another. Cetuximab, a chimeric mouse-human IgG1 monoclonal antibody against epidermal growth factor receptor, contains the alpha-gal epitope in its Fab arm portion and has been known to cause the alpha-gal allergy.¹¹

Additional medications, inactive ingredients, and procedures are also known to contain or utilize the alpha-gal epitope such as:

- Creon 10²
- Protein powders with whey²
- Xenograft surgery⁶

The issue with xenograft surgery has been resolved by using knock-out pigs lacking the alpha-gal epitope.⁴

To obtain information on animal by-product content, health care providers must contact manufacturers. Manufacturers do not currently report alpha-gal content in their package inserts or test for alpha-gal content in products. Inactive ingredient information can change at any time, and the FDA does not require manufacturers to disseminate this information. To prevent unnecessary exposure to alpha-gal, pharmacists should ensure that alpha-gal allergic patients avoid meat-containing medications. To provide timely patient care, alpha-gal information needs to be readily available, which is an area in which pharmacists can make an impact.¹⁰

Drug Information Service Contribution

At an academic medical center, a patient with the alpha-gal allergy with allergic reactions to antihypertensive medications presented to an immunologist.¹² The medications contained gelatin and magnesium stearate. The drug information service proceeded to create an alpha-gal content database to support the selection of an appropriate antihypertensive pharmacotherapy regimen for patients who have the alpha-gal allergy. Pharmacists contacted manufacturers with the broadest range of antihypertensive medications, and asked, “Do your products contain galactose-alpha-1,3-galactose, alpha-gal, mammalian meat, or any animal by-products?” No manufacturers tested for the presence of alpha-gal in their product, but animal by-product content was available. All manufacturers took more than 24 hours to respond, and some required 1 or more call-back attempts.

Based on correspondence with manufacturers, the Table lists medications that do not contain animal by-products, suggesting they are alpha-gal-free. The drug information service continues to review and add medications to its database. It has reviewed hyperlipidemia medications, narcotics, and dermatologic creams to date.

Table: Medications that Do Not Contain Animal By-products (per the manufacturer)

Medication	Manufacturer
Amlodipine	Qualitest
Atenolol	Mylan, Sandoz
Losartan potassium tablet, film coated	Sandoz
Valsartan tablet	Sandoz
Oxycodone liquid	Lannett
Clotrimazole	Natureplex

Although alpha-gal content cannot be completely ruled out, products without animal by-products theoretically may be used to safely treat patients with a documented alpha-gal allergy. One limitation of this database is that manufacturers do not routinely test for alpha-gal, so definitive conclusions cannot be drawn. However, the lack of information is intrinsic to the subject matter and not a database flaw.

The rising incidence and the serious nature of the alpha-gal allergy underscores the importance of properly managing patients. There is a need for more information on this topic. This database simplifies the task of verifying critical information and promotes timely decision making. The flexible design also allows for expansion to offer a complete reference. In the future, this database aims to compile all alpha-gal-related information into 1 central location for all medication classes.¹⁰

Conclusion

Pharmacists should be cognizant of patients presenting with anaphylaxis symptom, with a history of exposure to ticks and of consuming mammalian meats. The delay in symptom presentation may be attributed to the time required to digest meats. As pharmacists, knowing a patient's full history will enhance recognition of the allergy.

Resources for pharmacists include the Alpha-Gal Allergy Awareness Web site (www.alpha-gal.org). The Robert Wood Johnson University Hospital drug information service database is available for use by pharmacists by calling 732-937-8842.

Additional research is required on the effect of alpha-gal in medications for patients with the alpha-gal allergy. Pharmacists, especially in the emergency department and ambulatory care settings who see patients with tick bites, should be aware of this allergy and medication's potential to elicit symptoms.

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- See more at: <http://www.pharmacytimes.com/publications/issue/2015/may2015/alpha-gal-mammalian-meat-allergy-implications-for-pharmacists#sthash.EX5cmkG1.dpuf>

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Vanderbilt Asthma, Sinus, Allergy Program sees uptick in alpha-gal syndrome

by Tavia Smith (<http://news.vanderbilt.edu/author/taviasmith/>) | Thursday, Mar. 31, 2016, 12:35 PM



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Vanderbilt's Asthma, Sinus and Allergy Program (<http://www.vanderbilthealth.com/asap/>) (A.S.A.P) has seen an increase in the number of patients being treated for alpha-gal syndrome, commonly known as the red meat allergy linked to tick bites.

Just five years ago, the number of patients diagnosed and treated for alpha-gal was minimal. Allergists at A.S.A.P. have diagnosed and are currently treating approximately 160 patients with alpha-gal syndrome.

The increase is attributed to improved understanding of how alpha-gal syndrome presents as well as improved diagnostic testing.

"Alpha-gal syndrome has only recently been completely described (in the late 2000s) and was more clearly described over the last decade," said [Andrew S. Nickels](https://medicine.mc.vanderbilt.edu/person/andrew-s-nickels-md) (<https://medicine.mc.vanderbilt.edu/person/andrew-s-nickels-md>), M.D., assistant professor of Medicine and Pediatrics and an allergist at A.S.A.P.

"More doctors are becoming aware of this syndrome and once identified, more tests have become commercially available for allergist to order for their patients."

Alpha-gal is short for Galactose-alpha-1,3-galactose. This molecule is a carbohydrate molecule found in mammalian meats, most commonly cow, lamb and pork.

Hives, swelling of the lips, eyes, tongue, throat, respiratory issues, vomiting, diarrhea, increased heart rate and low blood pressure are common reactions to alpha-gal. Yet, while typical food allergies may cause a reaction within minutes, Alpha-gal creates a delayed reaction of three to six hours after exposure, making diagnosis more difficult.

In 2009, the first reports of delayed anaphylaxis, a serious, life-threatening allergic reaction, from eating red meat were described. Within a year it was discovered it was more common than thought and by 2012 thousands of cases across large areas of the southern and eastern U.S. were reported, according to a National Institutes of Health journal article.

The underlying cause of contacting “alpha-gal” was linked to being bitten by a tick, most typically the lone star tick.

“The theory is that the ticks will feed on deer and then when they bite humans, the humans are exposed to the Galactose-alpha-1,3-galactose found in the deer blood still in the tick,” Nickels said. “The human’s immune system then develops molecules call “IgE” that are specific to the “alpha gal” allergen. Once this occurs, they are prone to have allergic reactions, Nickels said.

Alpha-gal does not have a cure that can lead patients to eating red meat again, but it can be treated.

Once diagnosed, allergists recommend strict avoidance of cow, pork and lamb, and some patients may also need to avoid mammalian organs such as kidney or liver, gelatins, and possibly even milk depending on the patient, Nickels said. Knowing how to treat allergic reactions if the patient accidentally eats an offending food is a major component of treatment. Epinephrine auto injectors (EpiPens) are recommended at the first sign of an allergic reaction, as well as emergency care to administer more epinephrine, antihistamines, and steroids, depending on the severity of the reaction, Nickels said.

Nickels said that prevention of “alpha-gal” syndrome, as well as other tick-borne disease such as Lyme disease, likely can be achieved by making every effort to avoid being bitten by ticks.

The Centers for Disease Control and Prevention recommends tips for avoiding ticks, including walking in the center of trails, avoiding wooded or overgrown areas where ticks are more likely to live, using Permethrin treated boots and clothing during camping or hunting trips, and using DEET containing bug repellents on the skin.

Patients having symptoms such as hives, swelling of the lips or the eyes, respiratory symptoms like coughing or wheezing, or other symptoms that could be related to allergic reactions should see a Board Certified Allergy/Immunology provider to discuss their symptoms and possible testing “alpha-gal” syndrome.

A.S.A.P. has several specialists who have expertise in this type of allergy.

VICC study of cancer drug led to alpha-gal discovery

The discovery of alpha-gal syndrome happened due to the diligent work of several doctors and researchers at Vanderbilt and several universities that began as an unrelated enigma surrounding an allergic reaction to a drug used in the treatment of cancer.

Jordan Berlin (<http://www.vicc.org/dd/display.php?person=jordan.berlin>), M.D., professor of Medicine, Ingram Professor of Cancer Research and co-director of Phase I Research at Vanderbilt-Ingram Cancer Center (VICC) noted that cetuximab, a drug used in the treatment of colorectal cancer, caused a severe allergic reaction shortly after being infused in patients in some parts of the United States primarily Tennessee, Arkansas and North Carolina.

Christine Chung, M.D., a former assistant professor of Medicine and Cancer Biology and VICC researcher, led the study in her lab with the results published in the *New England Journal of Medicine*. VICC researchers along with doctors from the University of Virginia, Stanford, Duke, Harvard and the Allergy and Asthma Clinic of Northwest Arkansas, along with Bristol-Myers Squibb and ImClone Systems, the drug’s manufacturers, discovered these patients were having a severe reaction, because they already had the pre-existing antibody, immunoglobulin E or IgE, present in their body.

The research concluded that a 21.6 percent rate of IgE antibody to a glycoprotein, which is added in the manufacturing process to the cetuximab molecule, was present. That is what caused the allergic infusion reaction. The investigation of those cases established that the reaction was causally related to pre-existing IgE antibodies.

A previous VUMC Reporter story on red meat allergies and the lone star tick is here. (<http://news.vanderbilt.edu/2014/02/red-meat-allergies-likely-result-of-lone-star-tick/>)

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HEALTH APR 20 2016, 5:18 PM ET

Tick Bite Linked to Rise in Red Meat Allergies. Why Now?

by LINDA CARROLL

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The painful reaction started in the middle of the night. September Norman of Hendersonville, Tennessee, remembers waking up "itching like a fiend."

"I thought something had bitten me and I tried drinking water to flush it out," she says. A couple of hours later, her lips and tongue swelled up. Frightened, she woke her husband. "He took one look at me and said we have to go get help." EMS workers later told Norman she might have died if she'd gone without treatment for another 20 minutes.

Once doctors learned that Norman, 56, had been bitten by a tick and had eaten a steak for dinner, she was tested for antibodies to a carbohydrate molecule named alpha-gal, which has been implicated in tick-related meat allergies. She tested positive.

A tick-related meat allergy has been quietly spreading across the southern and eastern U.S. over the past two decades, but in recent years the number of cases have steadily risen. A tick bite in some people can kick off a sensitivity to red meat that can result in symptoms such as itching, hives, swollen lips and breathing problems. The reaction can sometimes be life threatening.

"We know at this point that there are over 3,500 cases," says Dr. Scott Commins, an associate professor of medicine and pediatrics in the division of rheumatology, allergy & immunology at the Thurston Research Center at the University of North Carolina, Chapel Hill. "I think there are many more."

The Centers for Disease Control and Prevention doesn't have data on the number of people who have developed the allergy, but Commins estimates that in the areas where the lone star tick is common, 1 to 5 percent will develop it. At UNC alone, there are 350 patients with the allergy, known as alpha-gal syndrome. "I know of a practice in Kentucky that has over 100 cases and there is a group down in Georgia near Savannah that has over 50 cases," Commins says.

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Lone Star Tick
(*Amblyomma americanum*)

ABOUT THIS MAP: This map shows the extent of established *Amblyomma americanum* tick populations, commonly known as lone star ticks. However, tick abundance within this area varies locally. The map does not represent the risk of contracting any specific tickborne illness. Please consult your local health department or USDA Cooperative Extension office to learn about the risks of tickborne disease in your local area. Rev. 07/2011.



Spread of the Lone Star tick. CDC

At Vanderbilt University, the syndrome was rarely seen a few years ago. Now, the university's doctors are treating 160 patients with the syndrome.

RELATED: Tick-related meat allergies surge in the Southwest

Scientists currently believe lone star ticks pick up alpha-gal after biting a deer, says Dr. Andrew Nickels, an assistant professor of medicine and pediatrics at Vanderbilt.

When the tick later bites a human, it passes along the alpha-gal, a substance found in all red meats, including beef, pork, lamb and venison.

It's thought that in some people the immune system spots alpha-gal as soon as it enters the blood stream and flags the unfamiliar molecule as an enemy invader.

When someone is sensitized to alpha-gal, meat consumption can lead to a host of symptoms, which can include hives; swollen lips, eyes, tongue and throat; respiratory issues; vomiting; diarrhea; increased heart rate and low blood pressure.

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"SOME JUST GET TERRIBLE STOMACH UPSET AND BAD ABDOMINAL CRAMPING SIX HOURS AFTER EATING BEEF."

Diagnosis of alpha-gal syndrome can be difficult because the allergic reaction is delayed — three to six hours after exposure, compared to minutes for other food allergies.

Also, some people don't have obvious allergic symptoms.

"Some just get terrible stomach upset and bad abdominal cramping six hours after eating beef," Commins says. "We are concerned these patients are not coming in to get medical attention."

RELATED: Why food allergies are on the rise: Are we too clean?

There are a lot of unanswered questions about the syndrome.

"We don't know if there is a predisposition that some people have that makes them more likely to develop an allergy after being bitten," says Dr. Anesh Adalja, an infectious disease specialist at the University of Pittsburgh Medical Center. "We don't know how many times someone has to be bitten before they develop the allergy. The lone star tick has been around for a long time and people have been bitten for a long time. Why are we seeing this now?"

Although there is no cure for the syndrome, some people seem to recover if they aren't bitten again by a tick, Commins says. Those who remain sensitized are told to avoid all red meats and gelatins, and in some patients, even dairy foods.

"WE DON'T KNOW IF THERE IS A PREDISPOSITION THAT SOME

35



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PEOPLE HAVE THAT MAKES THEM MORE LIKELY TO DEVELOP AN ALLERGY AFTER BEING BITTEN."

Some two years after the tick bite, Norman has become so sensitive she can't even handle meat to cook a meal for her family.

"It burns my hands," she says. "If I have chicken cooked on a grill where meat has been cooked, I have a reaction. It's hard to go out to eat because I have to go through my spiel and instead of cooking my chicken or fish on a grill they have to put it in a sauté pan."

She's realized that she can't leave anything to chance.

"I carry an EpiPen everywhere I go. I wear a medical alert bracelet because I am also allergic to gelatin and it is in a lot of IVs. If I were in a car accident and they put an IV in me, they could kill me. I can't take a flu shot or the shingles shot because they all contain gelatin. You have to be diligent and take care of your own health."

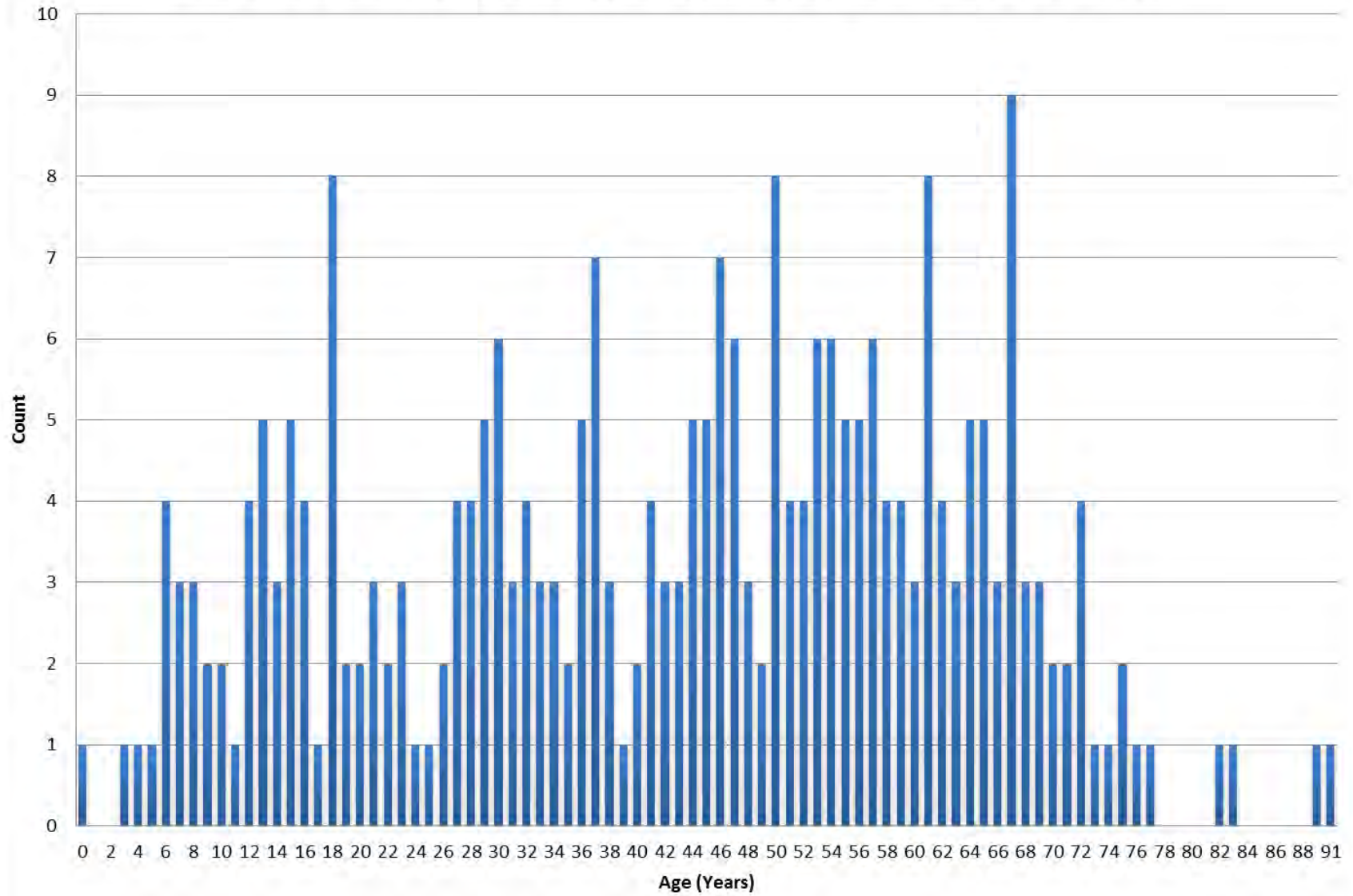
LINDA CARROLL 

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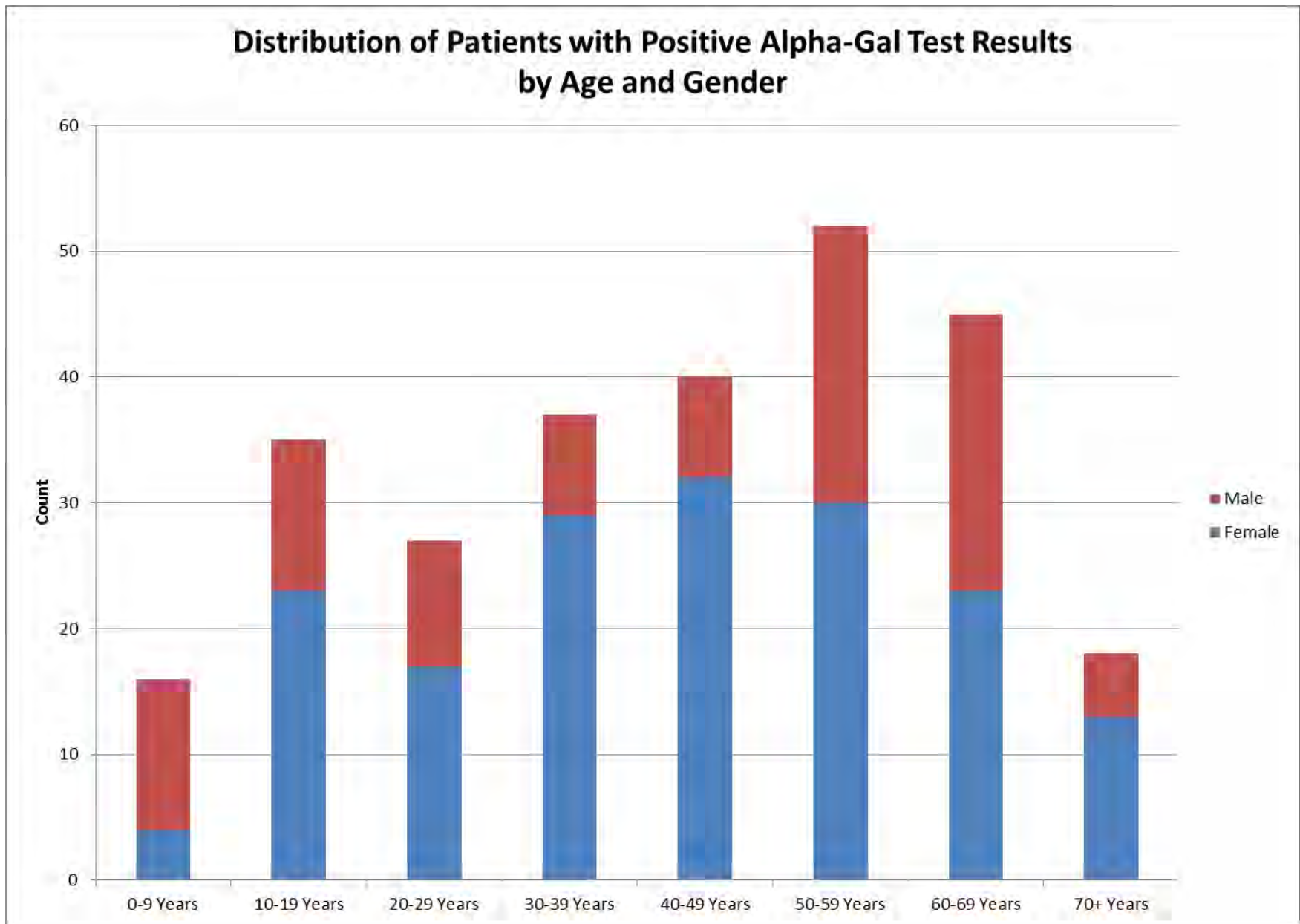
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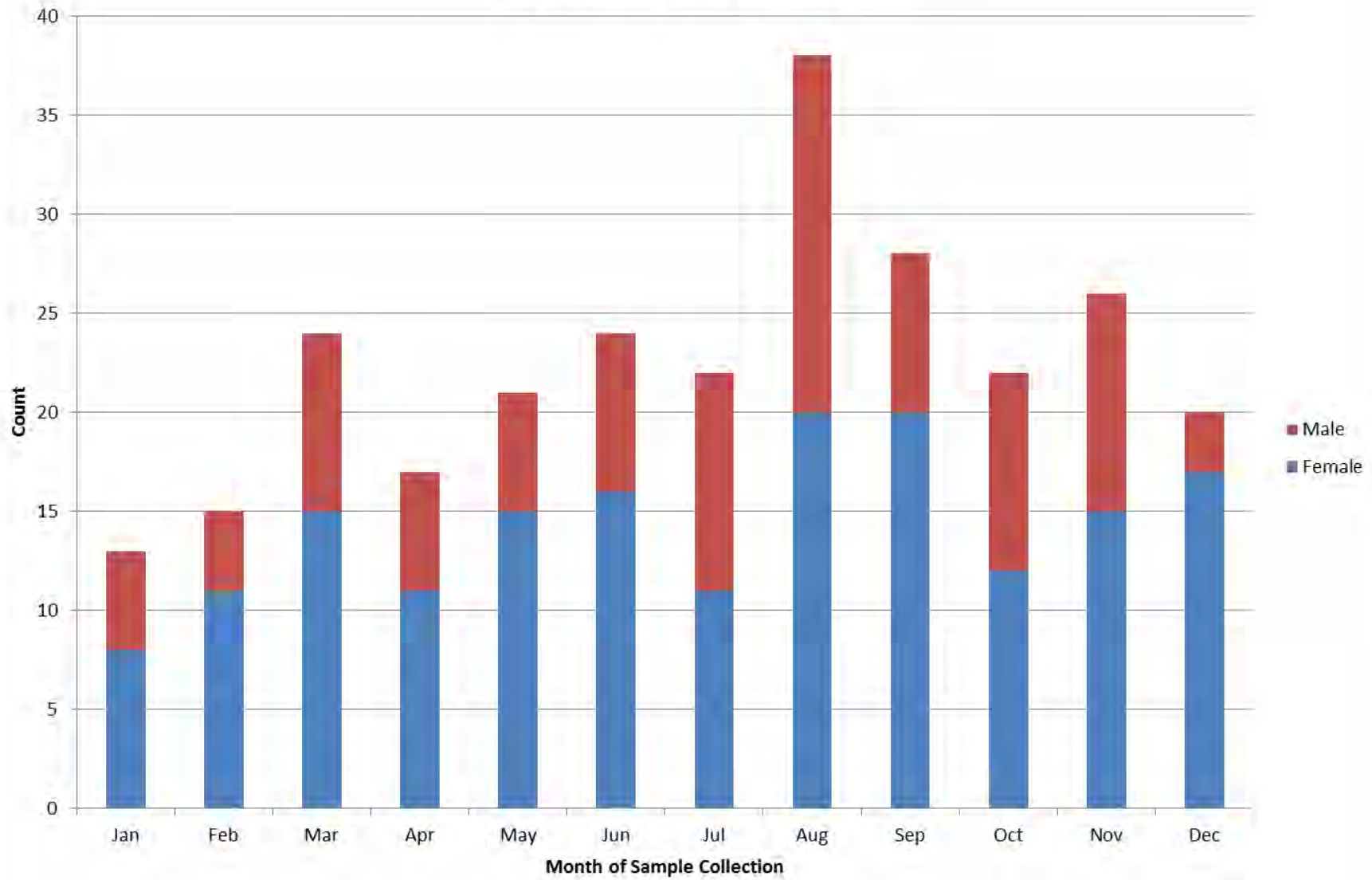
Age Distribution of Patients with Positive Alpha-Gal Test Results



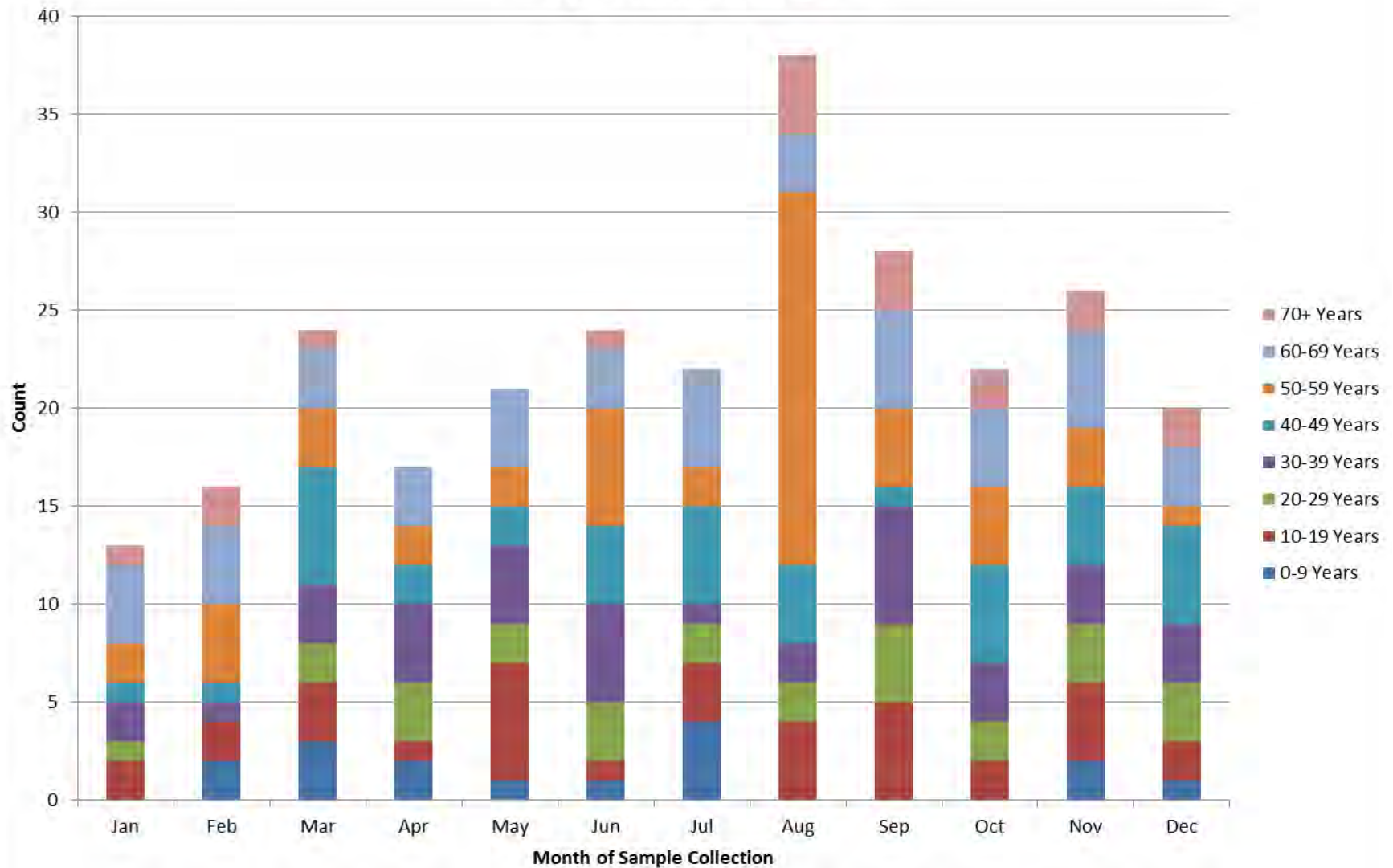
Distribution of Patients with Positive Alpha-Gal Test Results by Age and Gender



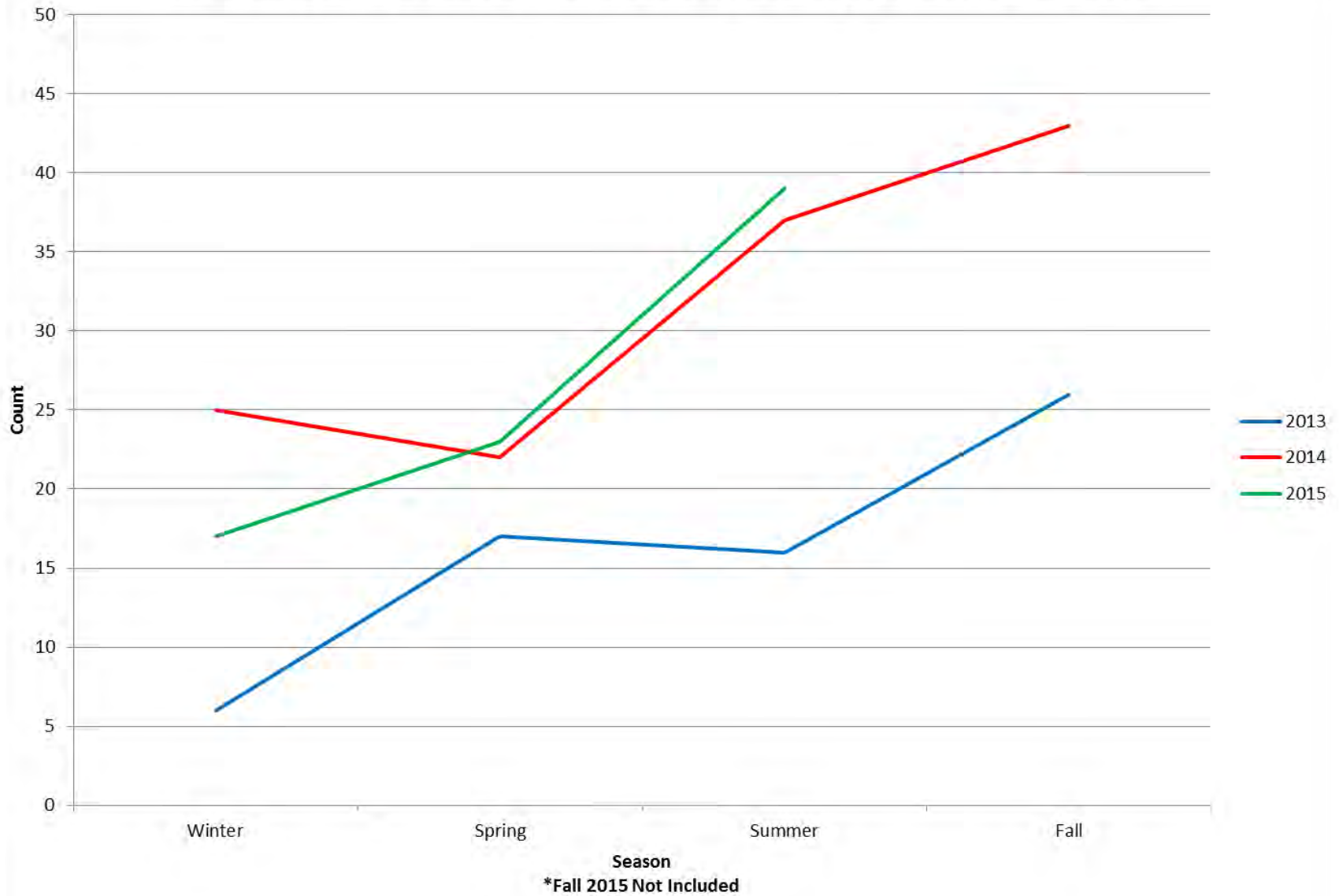
Distribution of Patients with Positive Alpha-Gal Test Results by Month and Gender



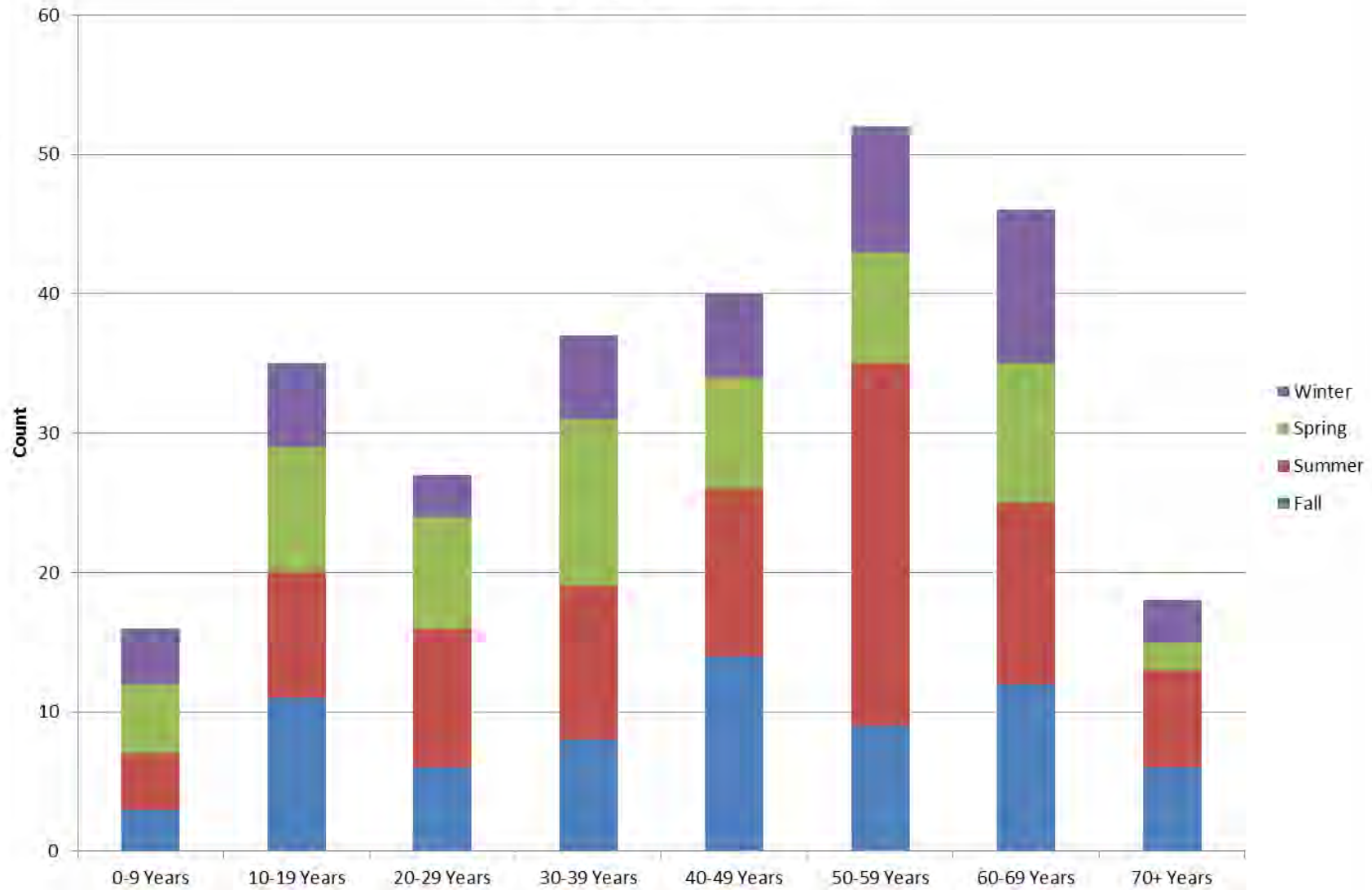
Distribution of Patients with Positive Alpha-Gal Test Results by Month and Age



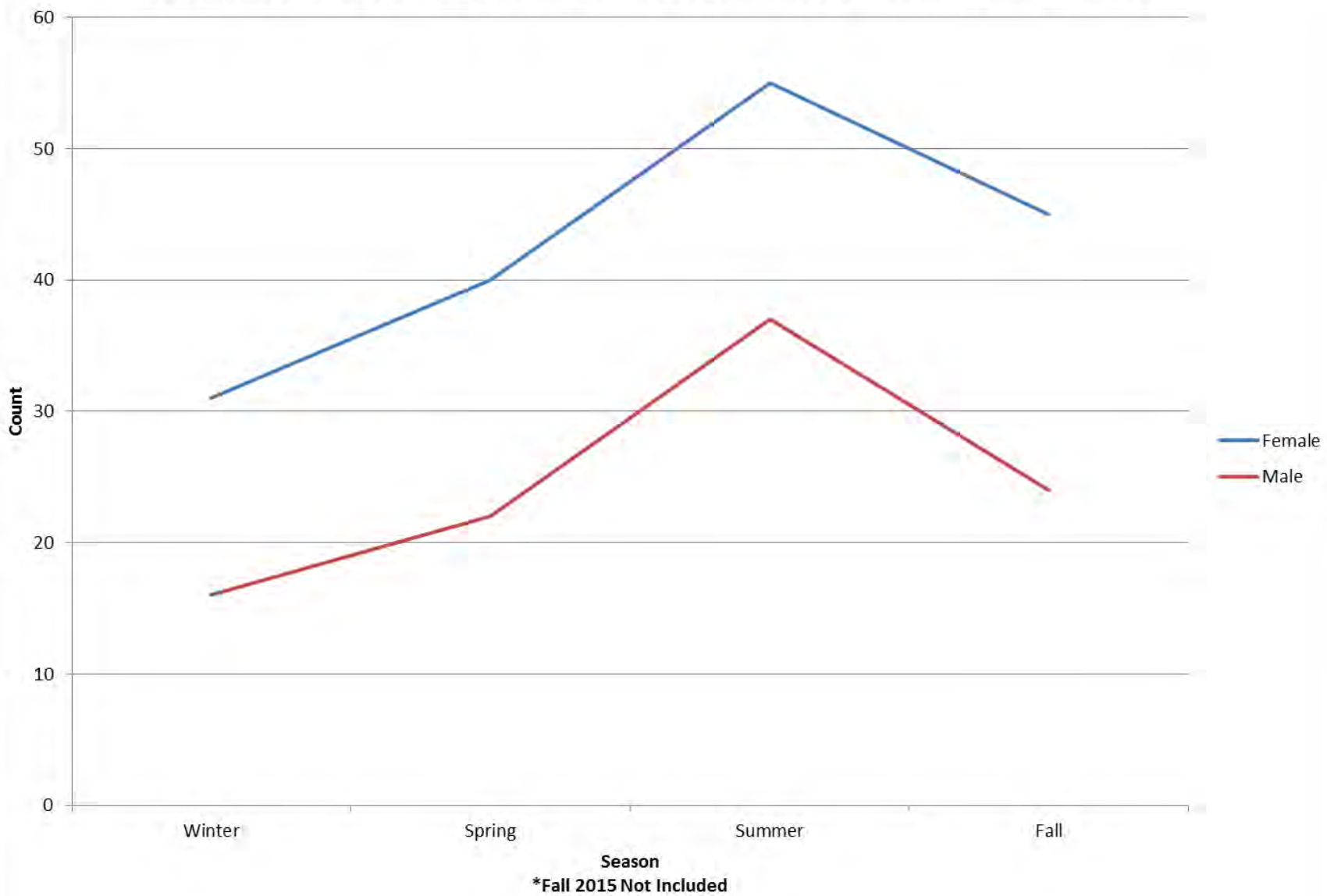
Patients with Positive Alpha-Gal Test Results by Season and Year



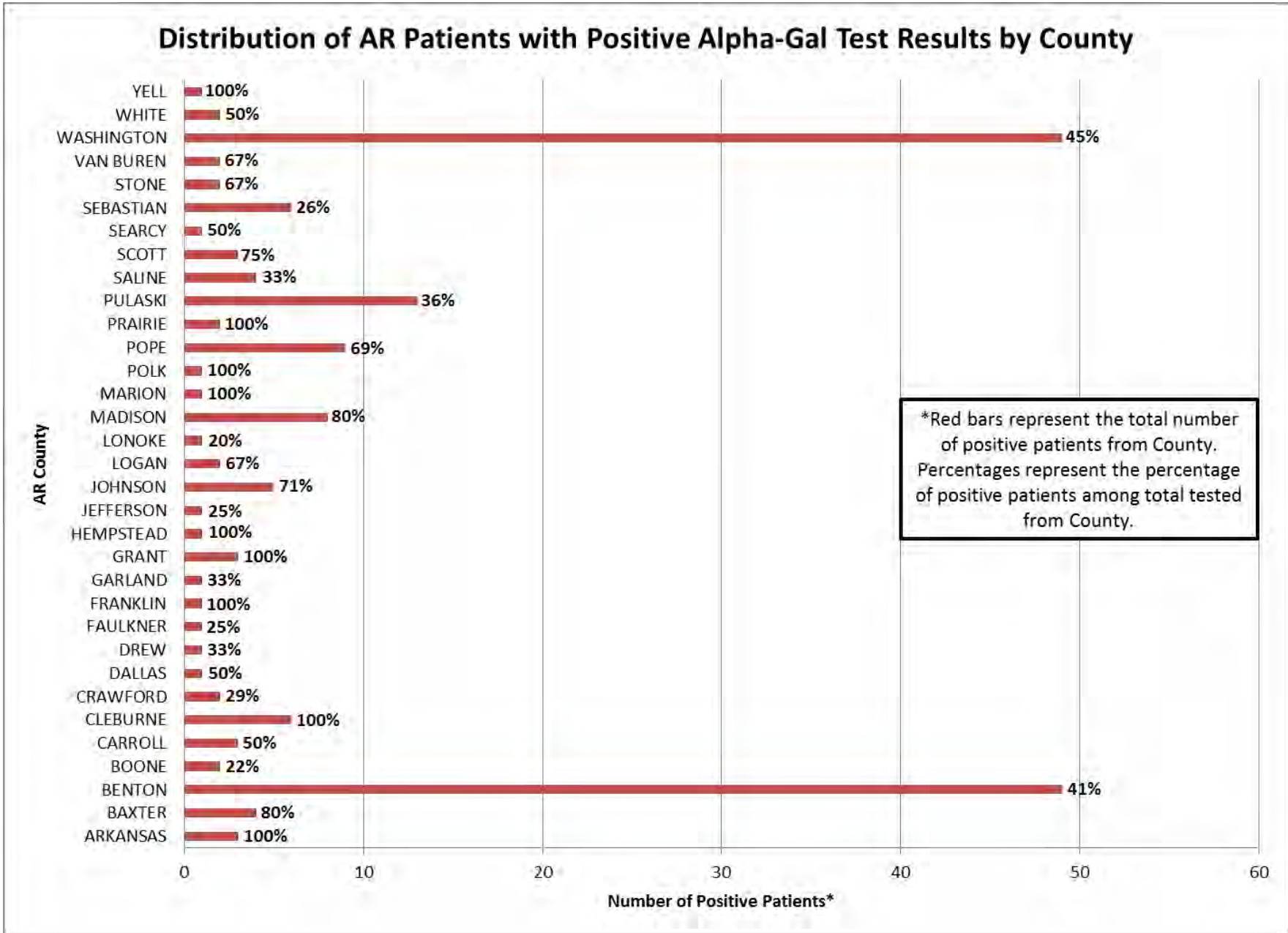
Distribution of Patients with Positive Alpha-Gal Test Results by Age and Season



Patients with Positive Alpha-Gal Test Results by Season and Gender



Distribution of AR Patients with Positive Alpha-Gal Test Results by County



IgE to Galactose 1,3- α -galactose in Arkansas

Tina Merritt, MD

Allergy & Asthma Clinic of NWA

Introduction

- 2000 ImClone asked Dr. Platts-Mills to develop a test for severe allergic reactions to Cetuximab
- 4 samples were positive for an allergy to something in the medication, ImClone did not get FDA approval
- 2006, a patient died in Bentonville from the first dose of Cetuximab
- I requested Dr. Platts-Mills develop a new test for this allergy
- 2008 Alpha-gal is identified as the epitope on cetuximab

ORIGINAL ARTICLE

Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose- α -1,3-Galactose

Christine H. Chung, M.D., Beloo Mirakhur, M.D., Ph.D., Emily Chan, M.D., Ph.D., Quynh-Thu Le, M.D., Jordan Berlin, M.D., Michael Morse, M.D., Barbara A. Murphy, M.D., Sharma M. Satinover, M.S., Jacob Hosen, B.S., David Mauro, M.D., Ph.D., Robert J. Slebos, Ph.D., Qinwei Zhou, Ph.D., Diane Gold, M.D., Tina Hatley, M.D., Daniel J. Hicklin, Ph.D., and Thomas A.E. Platts-Mills, M.D., Ph.D.

ABSTRACT

BACKGROUND

Cetuximab, a chimeric mouse-human IgG1 monoclonal antibody against the epidermal growth factor receptor, is approved for use in colorectal cancer and squamous-cell carcinoma of the head and neck. A high prevalence of hypersensitivity reactions to cetuximab has been reported in some areas of the United States.

METHODS

We analyzed serum samples from four groups of subjects for IgE antibodies against cetuximab: pretreatment samples from 76 case subjects who had been treated with cetuximab at multiple centers, predominantly in Tennessee, Arkansas, and North Carolina; samples from 72 control subjects in Tennessee; samples from 49 control subjects with cancer in northern California; and samples from 341 female control subjects in Boston.

RESULTS

Among 76 cetuximab-treated subjects, 25 had a hypersensitivity reaction to the drug. IgE antibodies against cetuximab were found in pretreatment samples from 17 of these subjects; only 1 of 51 subjects who did not have a hypersensitivity reaction had such antibodies ($P < 0.001$). IgE antibodies against cetuximab were found in 15 of 72 samples (20.8%) from control subjects in Tennessee, in 3 of 49 samples (6.1%) from northern California, and in 2 of 341 samples (0.6%) from Boston. The IgE antibodies were shown to be specific for an oligosaccharide, galactose- α -1,3-galactose, which is present on the Fab portion of the cetuximab heavy chain.

CONCLUSIONS

In most subjects who had a hypersensitivity reaction to cetuximab, IgE antibodies against cetuximab were present in serum before therapy. The antibodies were specific for galactose- α -1,3-galactose.

From the Division of Hematology/Oncology, Department of Medicine (C.H.C., E.C., J.B., B.A.M.), the Department of Cancer Biology (C.H.C., R.J.S.), and the Department of Otolaryngology (R.J.S.), Vanderbilt University School of Medicine, Nashville; Bristol-Myers Squibb, Plainsboro, NJ (B.M., D.M.); Stanford University School of Medicine, Menlo Park, CA (Q.-T.L.); the Department of Medicine, Duke University Medical Center, Durham, NC (M.M.); Asthma and Allergic Diseases Center, University of Virginia, Charlottesville (S.M.S., J.H., T.A.E.P.-M.); ImClone Systems, Branchburg, NJ (Q.Z., D.J.H.); Channing Institute, Harvard University, Boston (D.G.); and Allergy and Asthma Clinic of Northwest Arkansas, Bentonville (T.H.). Address reprint requests to Dr. Platts-Mills at the Asthma and Allergic Disease Center, University of Virginia Medical School, Box 801355, Charlottesville, VA 22908, or at tap2z@virginia.edu.

Drs. Chung and Mirakhur contributed equally to this article.

N Engl J Med 2008;358:1109-17.

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- Feb 2008 Patent application submitted for the test for Alpha-gal
- March 2008 NEJM article published about the allergy to cetuximab
- 2009 Dr. Platts-Mills bitten by ticks, and increased reports of beef/pork allergy
- 20+ years ago beef/pork allergy described in Australia related to tick bites

Amblyomma americanum courtesy of the CDC website



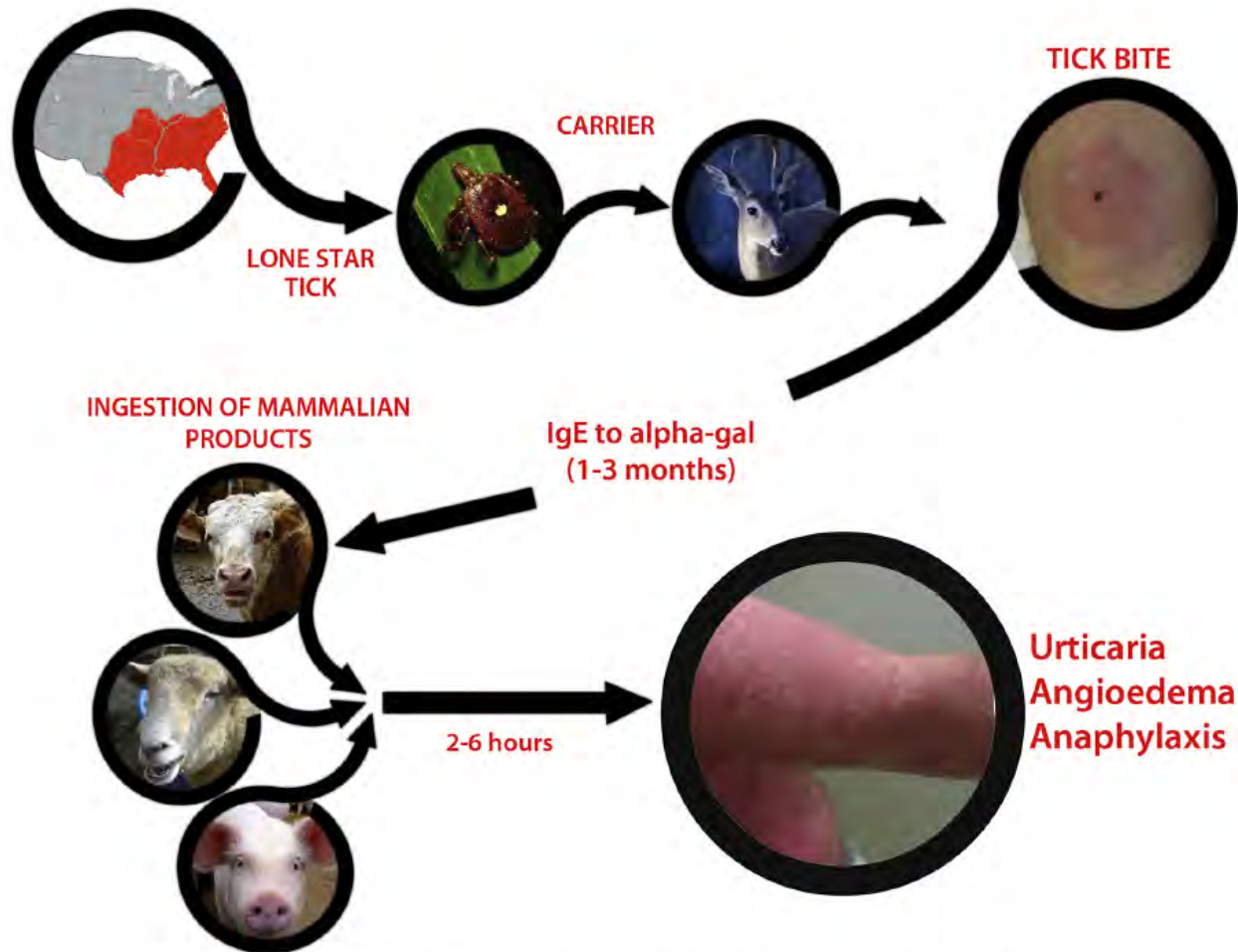
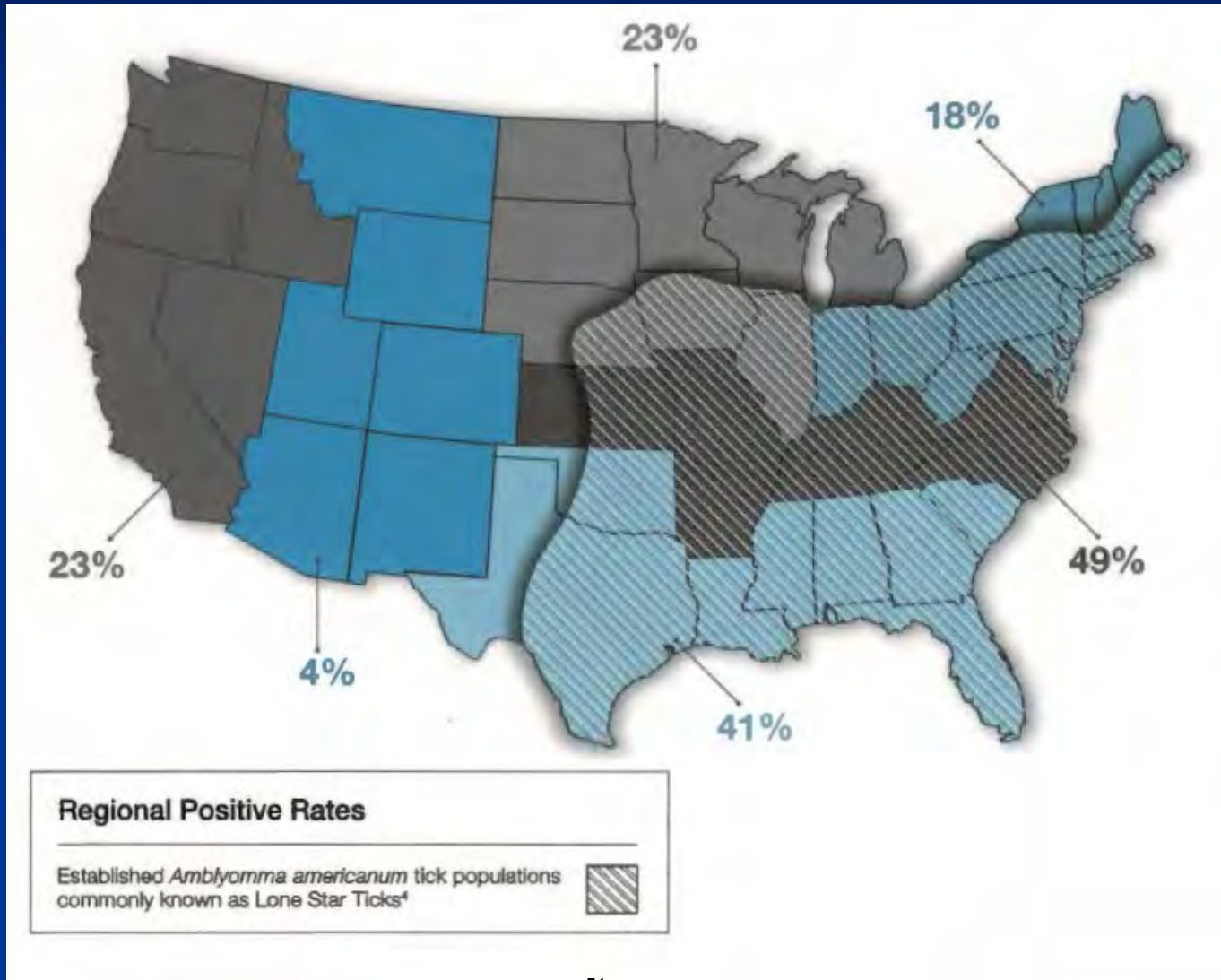
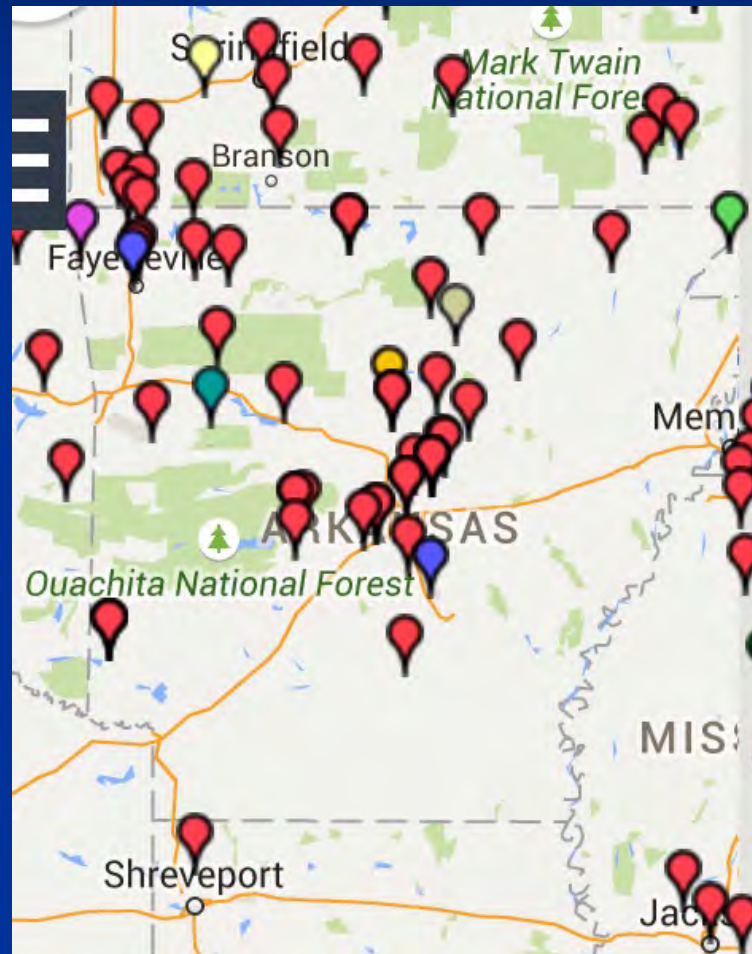


FIG 3. Summary of alpha-gal sensitization leading to clinical symptoms of red meat allergy. The southeastern section of the United States is where most of the reactions to red meat have been reported. This region overlaps with the distribution of the lone star tick. The current hypothesis is that persons are bitten by lone star ticks carried by deer into rural and urban areas. After a period of time, IgE to alpha-gal develops. Once IgE to alpha-gal reaches sufficient levels, ingestion of red meat can trigger reactions. Several of the images used in this figure are licensed under a Creative Commons CC BY-NC 2.0 (Attribution-NonCommercial 2.0 Generic) license (Cow: <https://flic.kr/p/adgjhp> by user Plashing Vole; Deer: <https://flic.kr/p/jeZwq7> by user Cherry Bream; Sheep: <https://flic.kr/p/4WirD> by user Lauren; Tick: <https://flic.kr/p/cdnNaY> by user Katja Schulz; Pig: <https://flic.kr/p/N7gpc> by user Anne).

(Map and picture courtesy of the ViroCor IBT Laboratories)



Map of Arkansas Alpha-gal support group



Conclusions

- In Arkansas thousands of people are positive for IgE to Alpha-gal (beef/pork/gelatin).
- Symptoms include anaphylaxis, urticaria, angioedema, gastrointestinal symptoms and atypical chest symptoms.
- Theories for the increase include rickettsial bacteria in the saliva of regional ticks, increased tick exposure, and exposure to pets.

Disclosures

- Dr. Tina Merritt has interest in the patent for the assay to measure IgE to chimeric monoclonal antibodies at the University of Virginia. PCT/US2008/054113.

Update on Alpha-gal (aka the Red Meat Allergy)

September 14, 2015



Photo credit: Sam Kittner '85

Scott P. Commins
Associate Professor



THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

DISCLOSURES

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Disclosures: NIH (research grant)

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Luis Matos
Saju Eapen
Dane McBride

MARHA



Did cetuximab cause her to sell Imclone stock too early...?



High Incidence of Cetuximab-Related Infusion Reactions in Tennessee and North Carolina and the Association With Atopic History

Bert H. O'Neil, Robert Allen, David R. Spigel, Thomas E. Stinchcombe, Dominic T. Moore, Jordan D. Berlin, and Richard M. Goldberg

High incidence of hypersensitivity reactions to cetuximab infusions in mid-Missouri:

Association with prior history of atopy

R. Owera, A. Gill, S. Haddadin, R. Khozouz and M. C. Perry

University of Missouri Columbia, Columbia, MO

JOURNAL OF
CLINICAL
ONCOLOGY

**Abstract, 2008 ASCO Annual Meeting Proceedings, Vol 26, No 15S,
2008:20747**

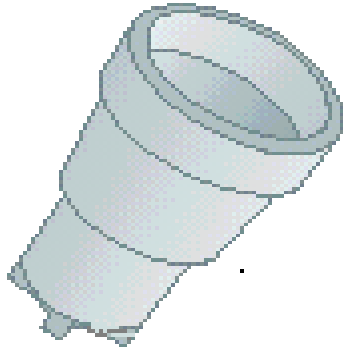


Regarding cetuximab HSR:

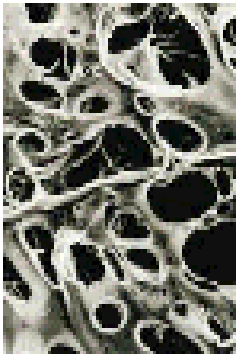
The story got stranger as O'Neil talked to more oncologists. He heard that a colleague in Nashville, Tennessee, was finding the same problem. But when O'Neil spoke to oncologists from other areas of the country, they didn't know what he was talking about. A prominent colorectal oncologist in New York "thought we were lying or crazy," O'Neil recalls.

From "A Mysterious Allergy Afflicts the South" by Sheila Read in *Endeavors*, 24:2, 2-3, 2008.

Measurement of IgE ab to Purified Allergens Using Streptavidin Solid Phase



“Allergen” of interest (cetuximab)
+ Biotin



Streptavidin Solid Phase + Biotinylated “Allergen”

Solid Phase*

Then add serum; wash; add labeled anti-IgE; detect chemilum.

*Routine assay technique in parallel with Phadia
standard curve gives results in IU/ml.⁶¹

Table 3. Specificity of the IgE Antibodies That Cross-React with Cetuximab.*

Type of Reaction and Subject No.	Type of Cetuximab†		Galactose- α -1,3-Galactose‡§	Mammalian Allergens				
	SP2/0‡	CHO‡		Mouse IgG‡ <i>international units per milliliter</i>	Cat	Dog	Fel d 1‡	Beef
Hypersensitivity reaction Anaphylaxis related to cetuximab								
1	41.6	0.35	13.8	0.35	3.16	2.60	0.35	3.02
2	38.8	0.35	35.2	0.35	13.20	12.30	0.35	12.46
3	20.2	0.35	12.6	0.35	9.34	9.77	0.35	6.92
4	11.1	0.35	2.9	0.35	1.94	1.86	0.35	1.82
5	4.9	0.35	2.0	0.35	0.35	0.35	0.35	0.35
6	4.2	0.35	2.7	0.35	1.54	1.50	0.35	1.66
Recurrent anaphylaxis unrelated to cetuximab¶								
7	131.0	1.89	38.9	1.75	41.50	34.50	3.64	32.90
8	69.2	0.35	42.1	1.19	27.70	32.00	0.35	26.20
9	55.1	0.35	32.2	0.43	22.20	25.10	0.35	13.80
10	43.5	0.35	32.3	0.35	37.30	29.40	0.35	3.48
11	81.1	0.35	100.0	0.35	14.30	14.70	0.35	8.75
12	13.0	0.35	9.0	0.78	8.86	8.84	0.35	8.90
Mean	27.7	NA	25.5	ND	10.30	9.93	NA	7.16
No hypersensitivity reaction¶¶	0	0	0	0	0	0	0	0

No alpha-gal

IgE to alpha-gal: a (very) brief history



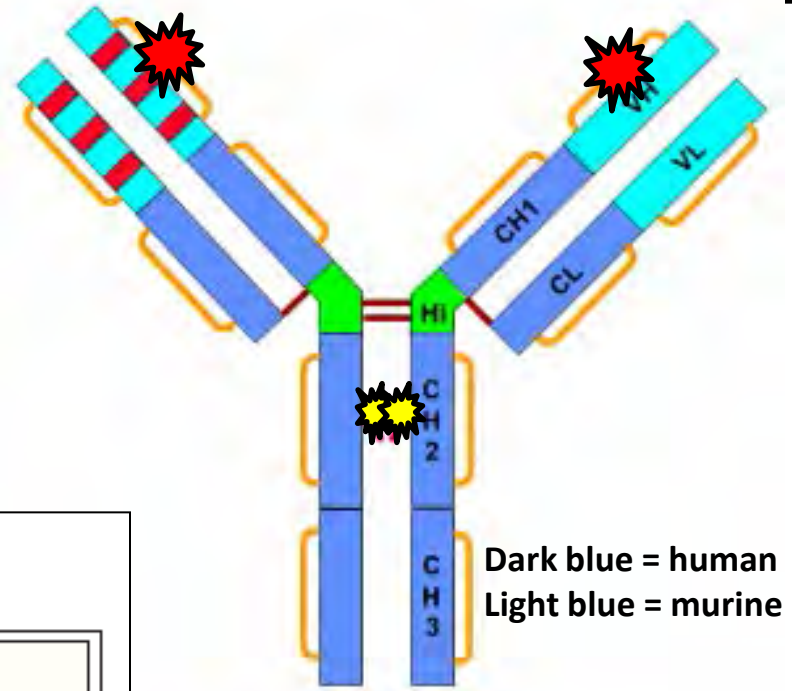
O'Neil et al,
JCO 2007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose- α -1,3-Galactose

Christine H. Chung, M.D., Beloo Mirakhur, M.D., Ph.D.,
Emily Chan, M.D., Ph.D., Quynh-Thu Le, M.D., Jordan Berlin, M.D.,
Michael Morse, M.D., Barbara A. Murphy, M.D., Shama M. Satinover, M.S.,
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Qinwei Zhou, Ph.D., Diane Gold, M.D., Tina Hatley, M.D.,
Daniel J. Hicklin, Ph.D., and Thomas A.E. Platts-Mills, M.D., Ph.D.



What is alpha-gal?

- Carbohydrate synthesized by the glycosylation enzyme alpha-1,3-galactosyltransferase
- **Alpha-gal is present on the tissues and cells of all lower mammals**
- Humans and apes, however, do not have alpha-gal due to an inactive gene product



Table 3. Specificity of the IgE Antibodies That Cross-React with Cetuximab.*

Type of Reaction and Subject No.	Type of Cetuximab†		Galactose- α -1,3-Galactose‡§	Mammalian Allergens					Beef
	SP2/0‡	CHO‡		Mouse IgG‡	Cat	Dog	Fel d 1‡		
<i>international units per milliliter</i>									
Hypersensitivity reaction									
Anaphylaxis related to cetuximab									
1	41.6	0.35	13.8	0.35	3.16	2.60	0.35	3.02	
2	38.8	0.35	35.2	0.35	13.20	12.30	0.35	12.46	
3	20.2	0.35	12.6	0.35	9.34	9.77	0.35	6.92	
4	11.1	0.35	2.9	0.35	1.94	1.86	0.35	1.82	
5	4.9	0.35	2.0	0.35	0.35	0.35	0.35	0.35	
6	4.2	0.35	2.7	0.35	1.54	1.50	0.35	1.66	
Recurrent anaphylaxis unrelated to cetuximab¶									
7	131.0	1.89	38.9	1.75	41.50	34.50	3.64	32.90	
8	69.2	0.35	42.1	1.19	27.70	32.00	0.35	26.20	
9	55.1	0.35	32.2	0.43	22.20	25.10	0.35	13.80	
10	43.5	0.35	32.3	0.35	37.30	29.40	0.35	3.48	
11	81.1	0.35	100.0	0.35	14.30	14.70	0.35	8.75	
12	13.0	0.35	9.0	0.78	8.86	8.84	0.35	8.90	
Mean	27.7	NA	25.5	ND	10.30	9.93	NA	7.16	
No hypersensitivity reaction	0	0	0	0	0	0	0	0	

Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose- α -1,3-galactose

Scott P. Commins, MD, PhD,^a Shama M. Satinover, MS,^a Jacob Hosen, BS,^a Jonathan Mozena, MD,^b Larry Borish, MD,^a Barrett D. Lewis, MD,^c Judith A. Woodfolk, MBChB, PhD,^a and Thomas A. E. Platts-Mills, MD, PhD^a *Charlottesville and Fredericksburg, Va, and Springfield, Mo*

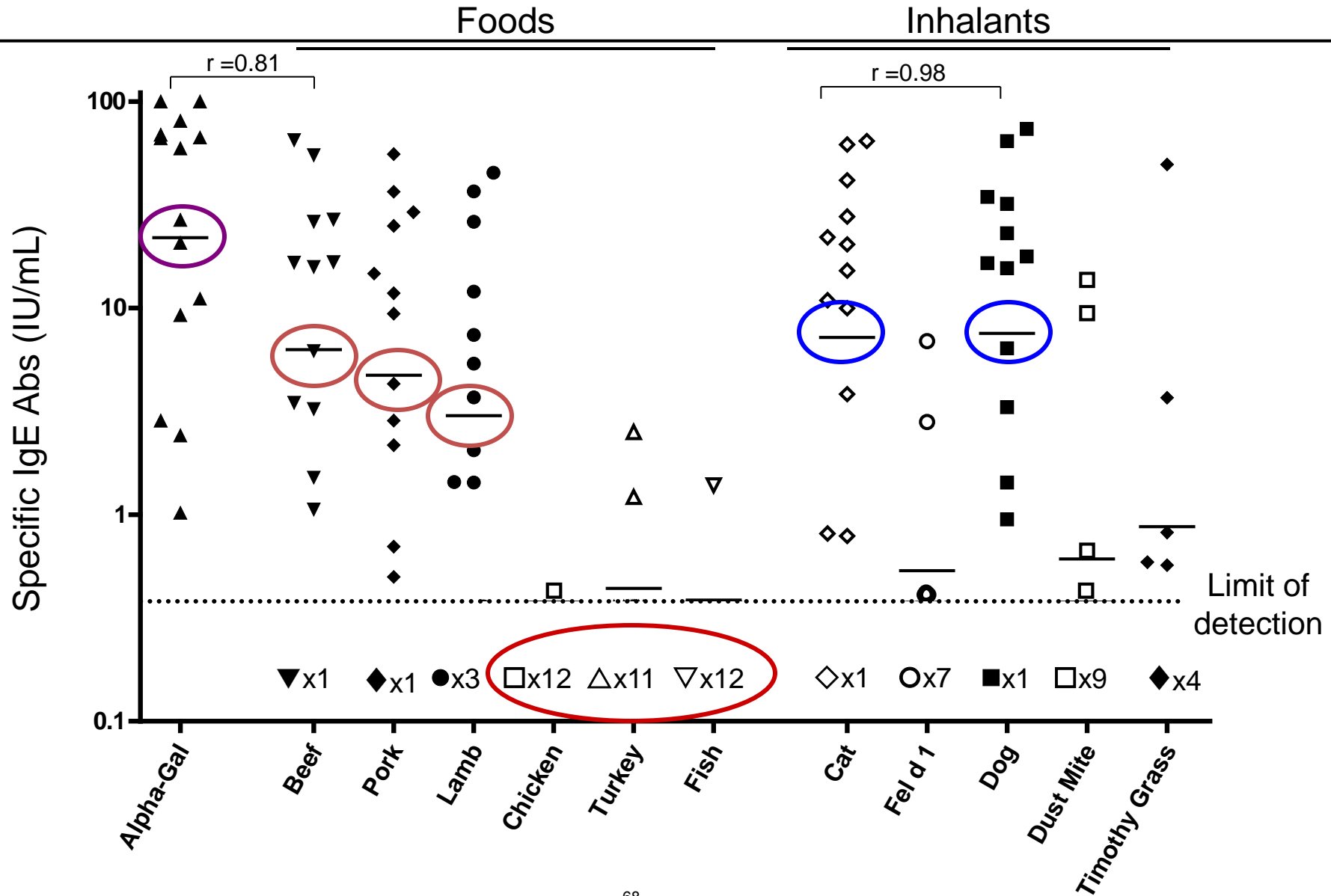
- 24 patients**
- Virginia & Missouri**
- Symptoms delayed 3-6 hours after eating mammalian meat**
- Prick skin test often less than 4mm**
- Intradermal skin test positive**

Skin Testing Results: Often $<4\text{mm}$ SPT



Prick test performed using lancette and intradermal testing with 25 gauge needle in the same patient on a single clinic visit.

Immunoassay of Specific IgE Abs in Patients with anti-Gal IgE

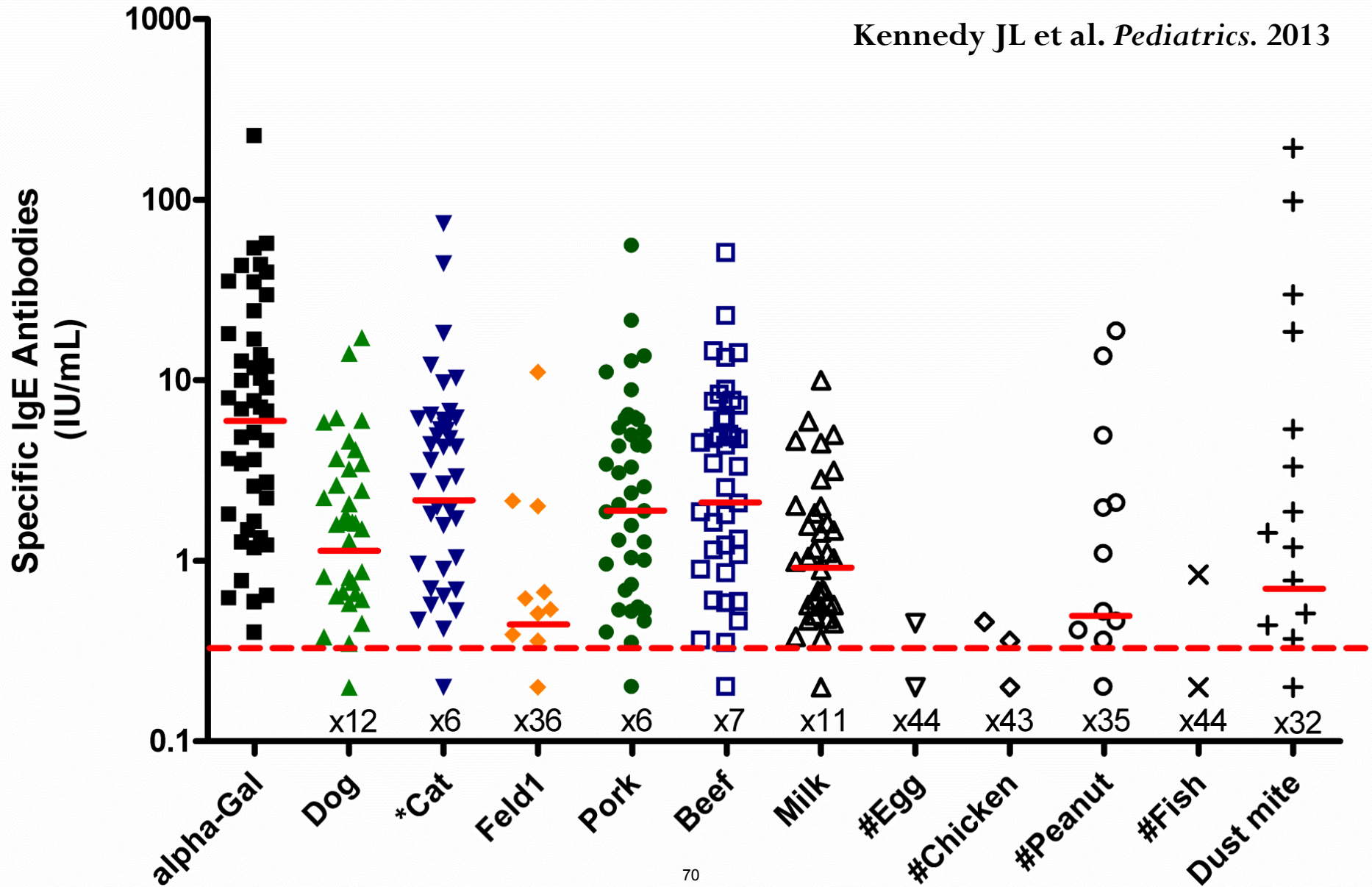


IgE Ab to alpha-gal in kids (n=45)

Sex (% male)	69%
Mean age at presentation (Range)	12 (4-17)
Geometric Mean of Total IgE (95% CI)	147 IU/mL (105-206 IU/mL)
Symptoms at presentation	
Anaphylaxis*	44%
Gastrointestinal/ Oral	64%
Urticaria	92%
Angioedema	31%
Average time to symptoms (Range)	4.68 hrs (10 mins to 24 hrs)
Tick exposure	100%
Redness and Itching at site of Tick bite	87%
Tick borne illness#	10%
Emergency Department (ED) visits	46% **
Medications administered in ED	Epinephrine (19%) Antihistamines (35%) Oral Steroids (19%) Parenteral Steroids (17%) IV Fluids (17%)
Hospital Admissions	8%

IgE Ab to alpha-gal in kids (n=45)

Kennedy JL et al. *Pediatrics*. 2013



MANAGEMENT

- Avoidance diet:
 - *Mammalian meat, esp fatty cuts (ice cream)*
 - *Dairy and cheese usually tolerated*
 - *Few issues with gelatin*
- Caution re: exercise, alcohol, recent tick bites
- Monitor IgE to alpha-gal over time
 - *Pork sausage (3) challenge when level declines signif.*

DEMONSTRATING THE DELAY



- Subject #FC-07: sIgE to alpha-gal = 9.3 IU/mL; Total IgE = 204
- Whole blood was collected, fixed & stained
- 6 hours after consuming 56g of pork sausage, subject released with (disappointing) mild itch and single hive

Subject calls from car 30 minutes after being released to report progression of itching and “warmth to skin”

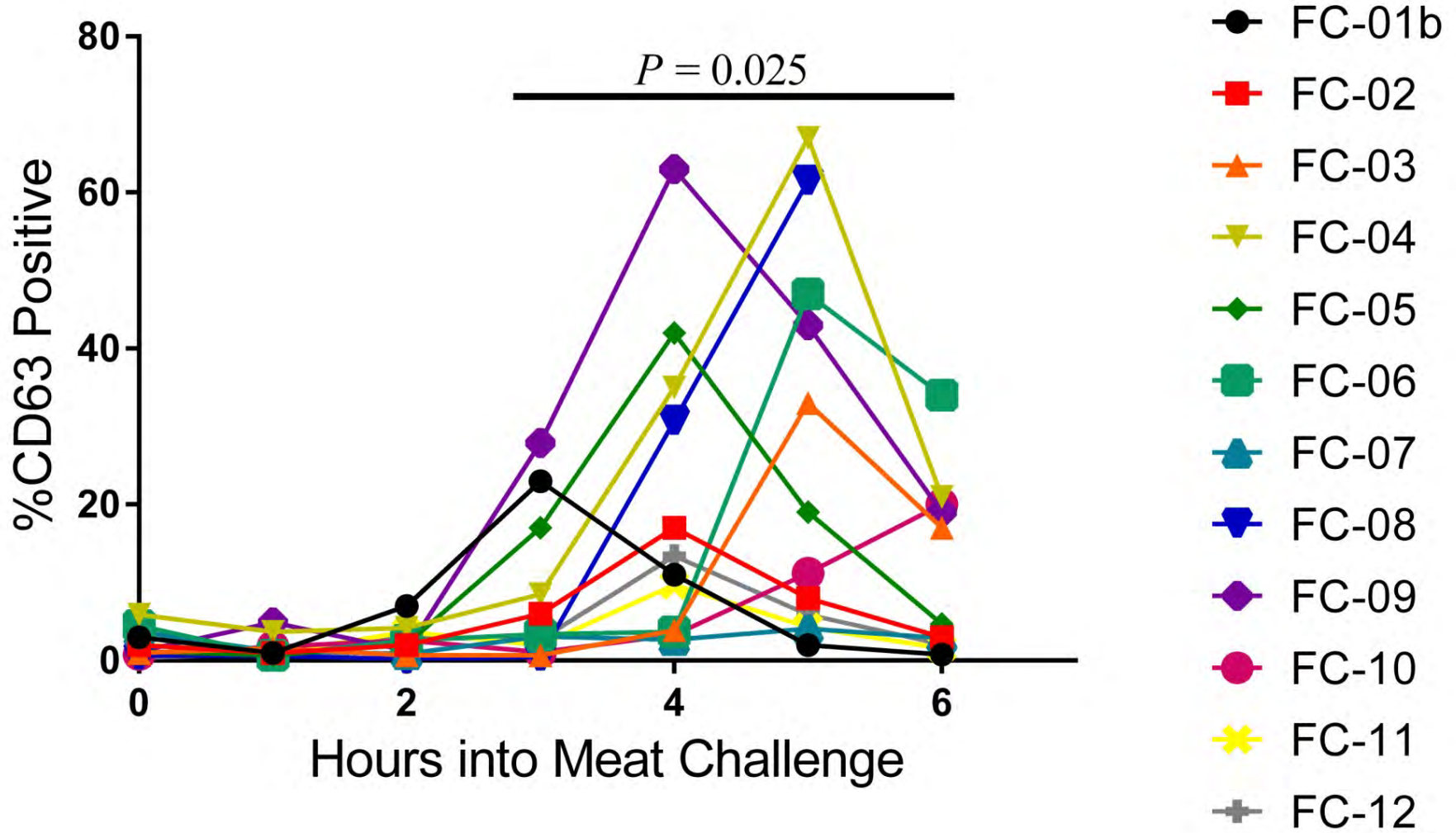


Initial picture upon arriving home (approximately 7.5 hours after eating pork sausage)

Approximately 8.25 hours after eating sausage



Basophil CD63 expression in individual subjects positive for IgE Ab over the course of a mammalian meat challenge



SUMMARY

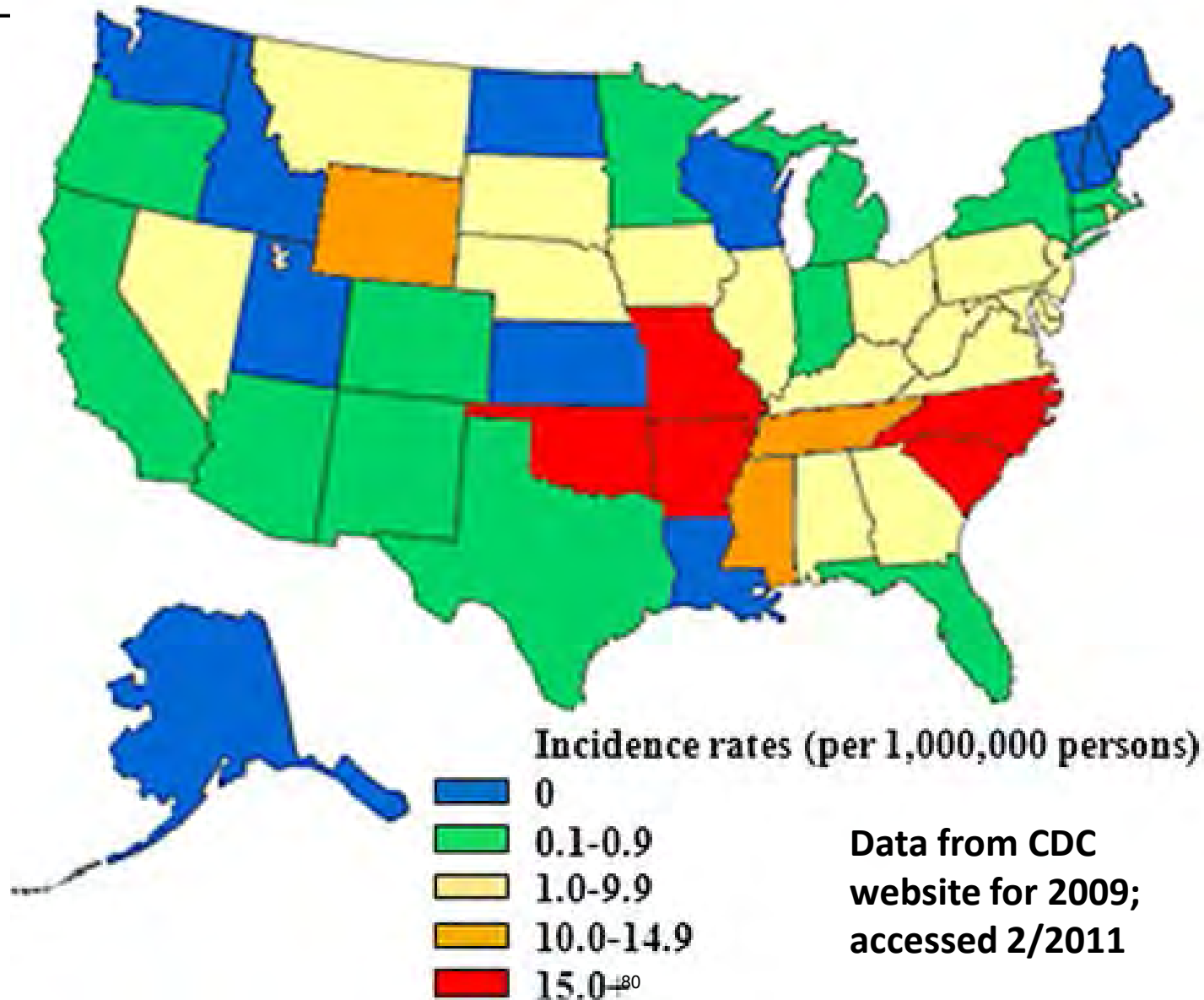
- Immunoassays more reliable than SPT for diagnosis
- Amount and type of meat are important
 - *Larger portion and fattier cuts produce reactions more consistently*
- Cofactors affect reaction severity and timing
 - *Exercise can reduce the delay and increase severity*

TICKS.
REALLY?

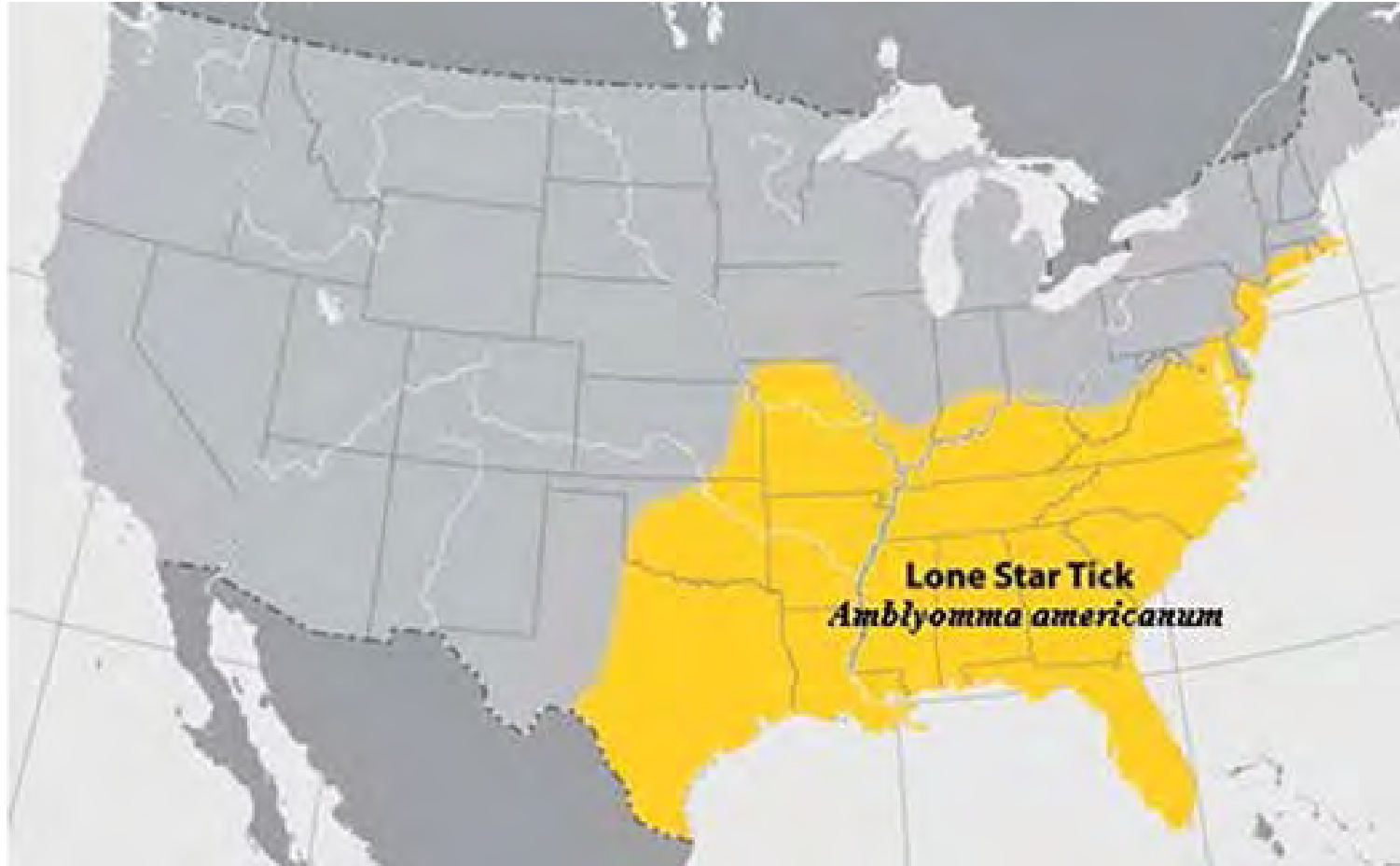
Geographical distribution of cetuximab hypersensitivity reactions



Geographical Incidence of Rocky Mountain Spotted Fever



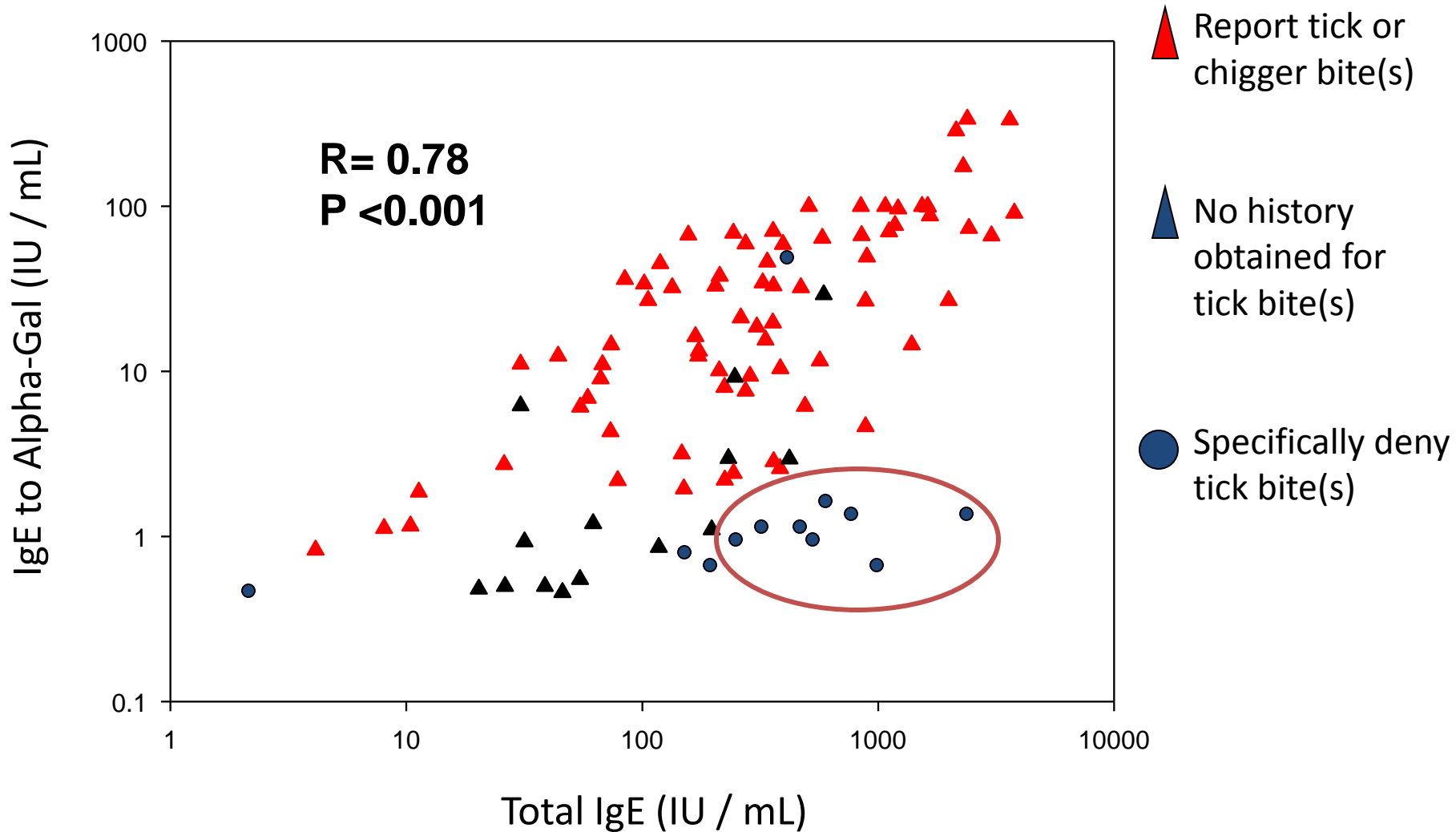
Geographical range of *Amblyomma americanum* population



Geographical range of *Amblyomma americanum* population



Total IgE versus IgE to Alpha-Gal



Bites from larval ticks and IgE to alpha-Gal



Test	5/21/07	10/9/07	11/6/07*
Alpha-Gal	negative	48.3	130
Total IgE	199	350	532

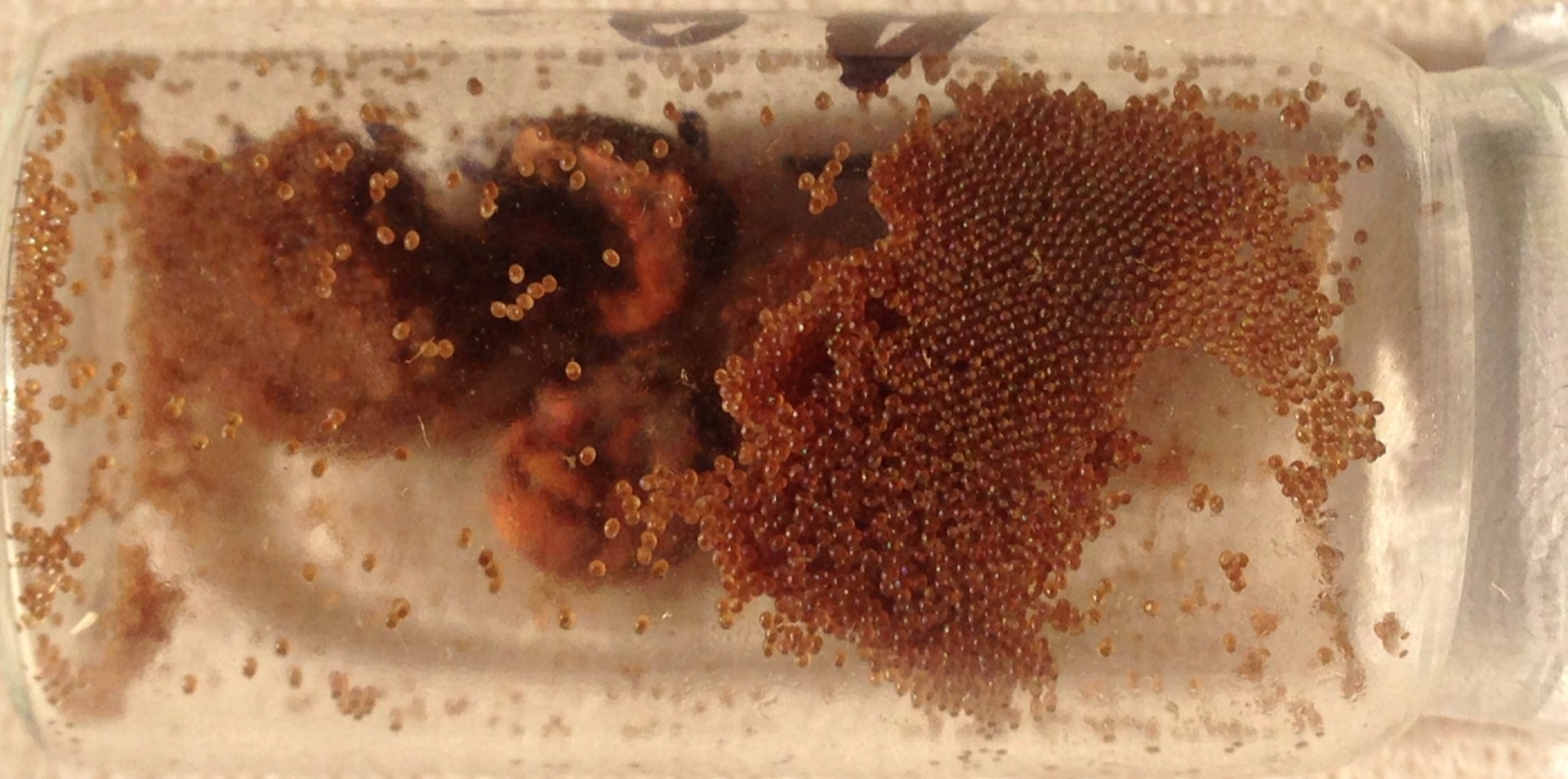
•Multiple bites by seed ticks are not uncommon in the Southeast.



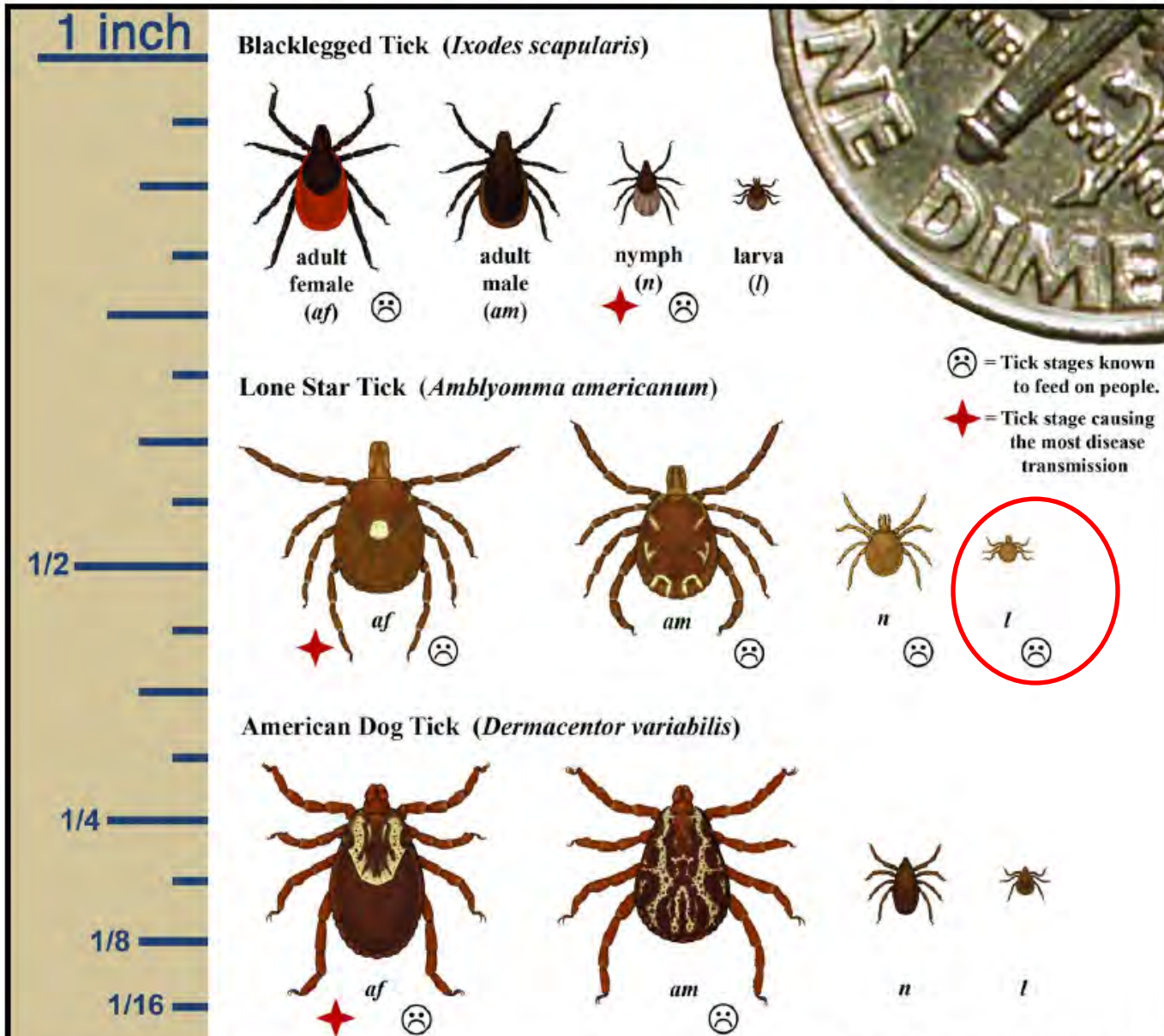
*Titers: Beef 19.2, Pork 10.1, Cat 17.5, Dog 19.8, IU/ml.
Chicken, Turkey, Roach, Dust Mite and Ragweed all <0.35 IU/ml.

Photograph: August 23, 2007.

LONE STAR TICKS: EGG CLUSTERS

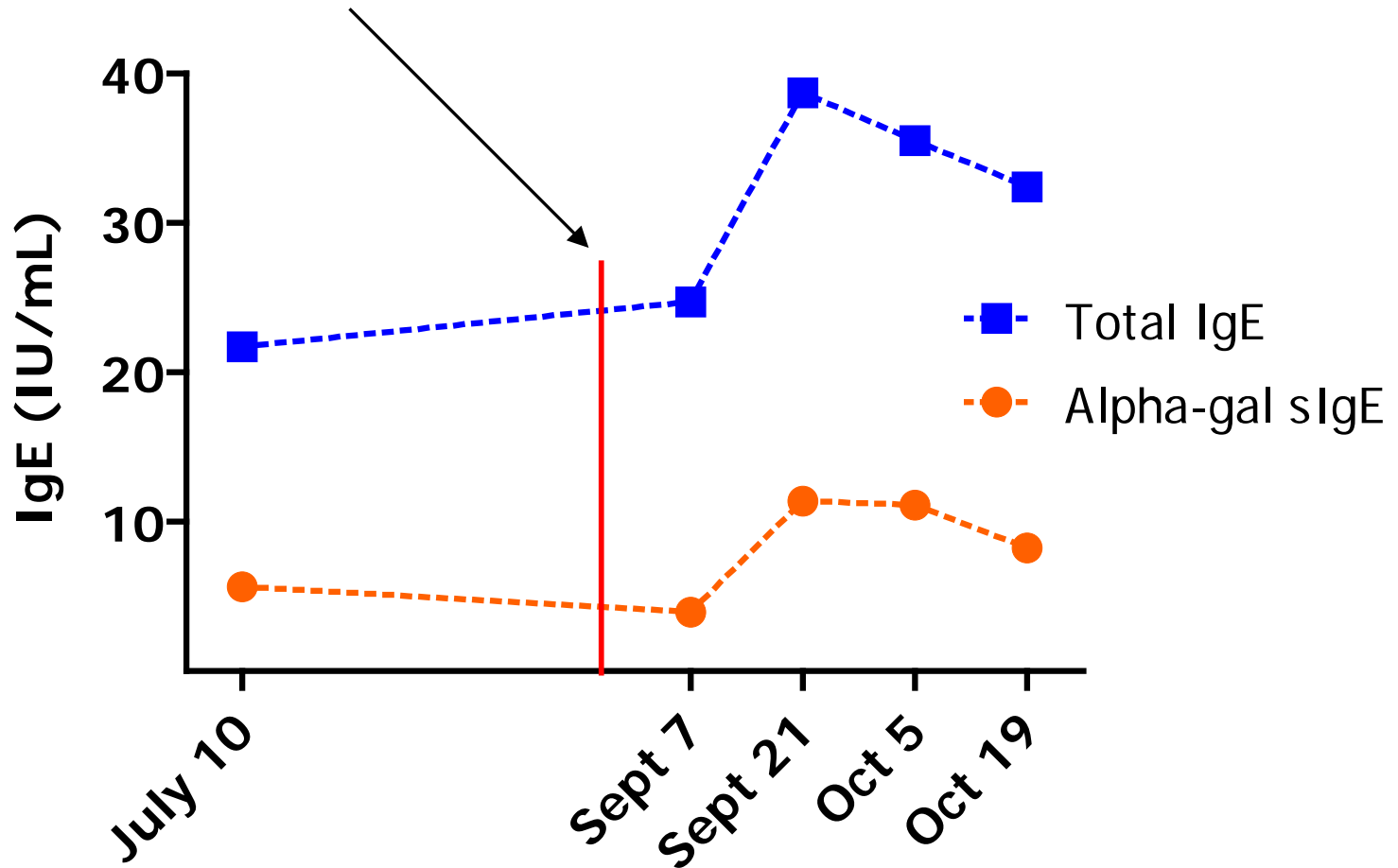


Tick Identification Chart

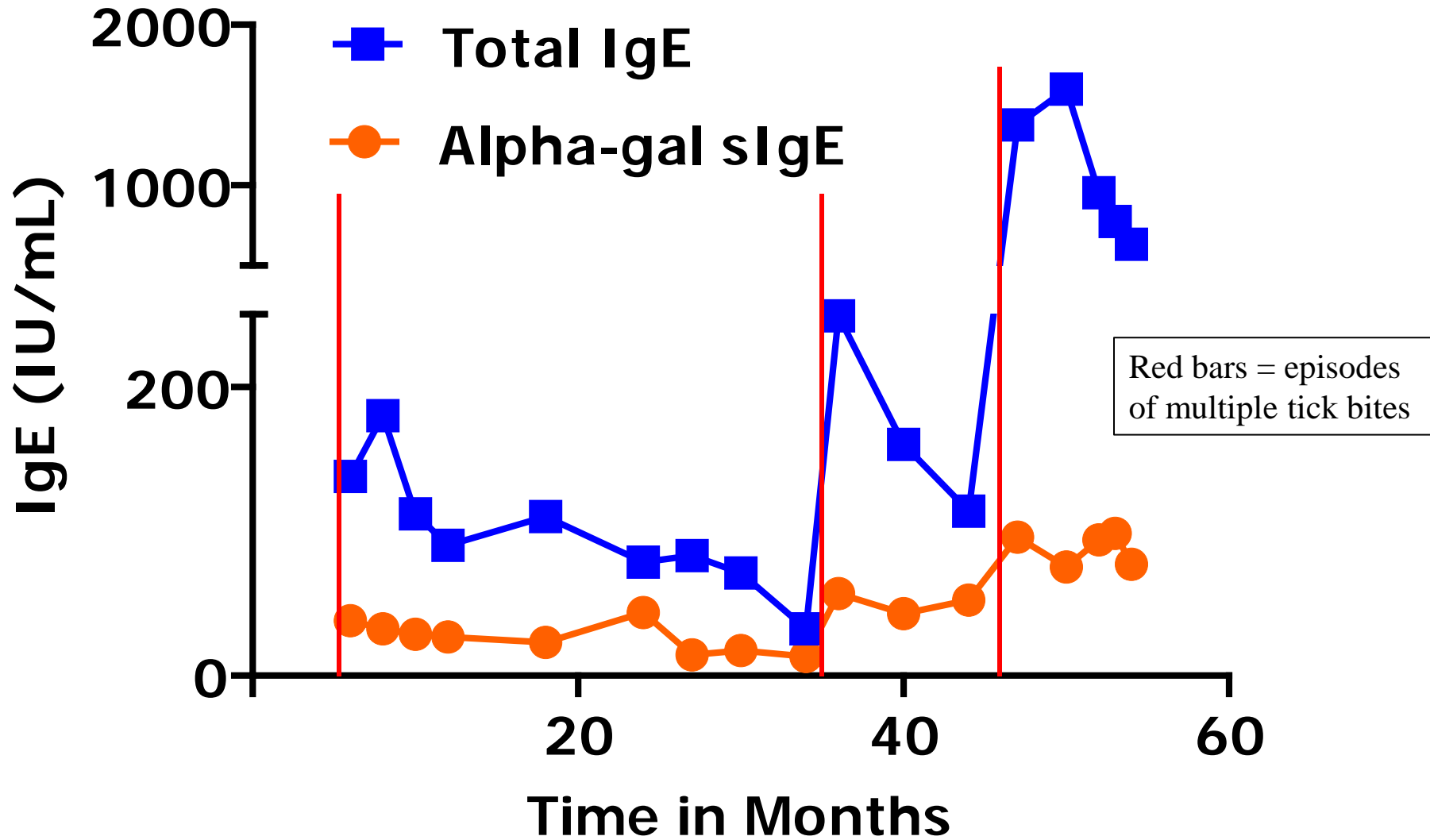


Original image: CDC; modified by D.N. Gaines for Virginia Department of Health

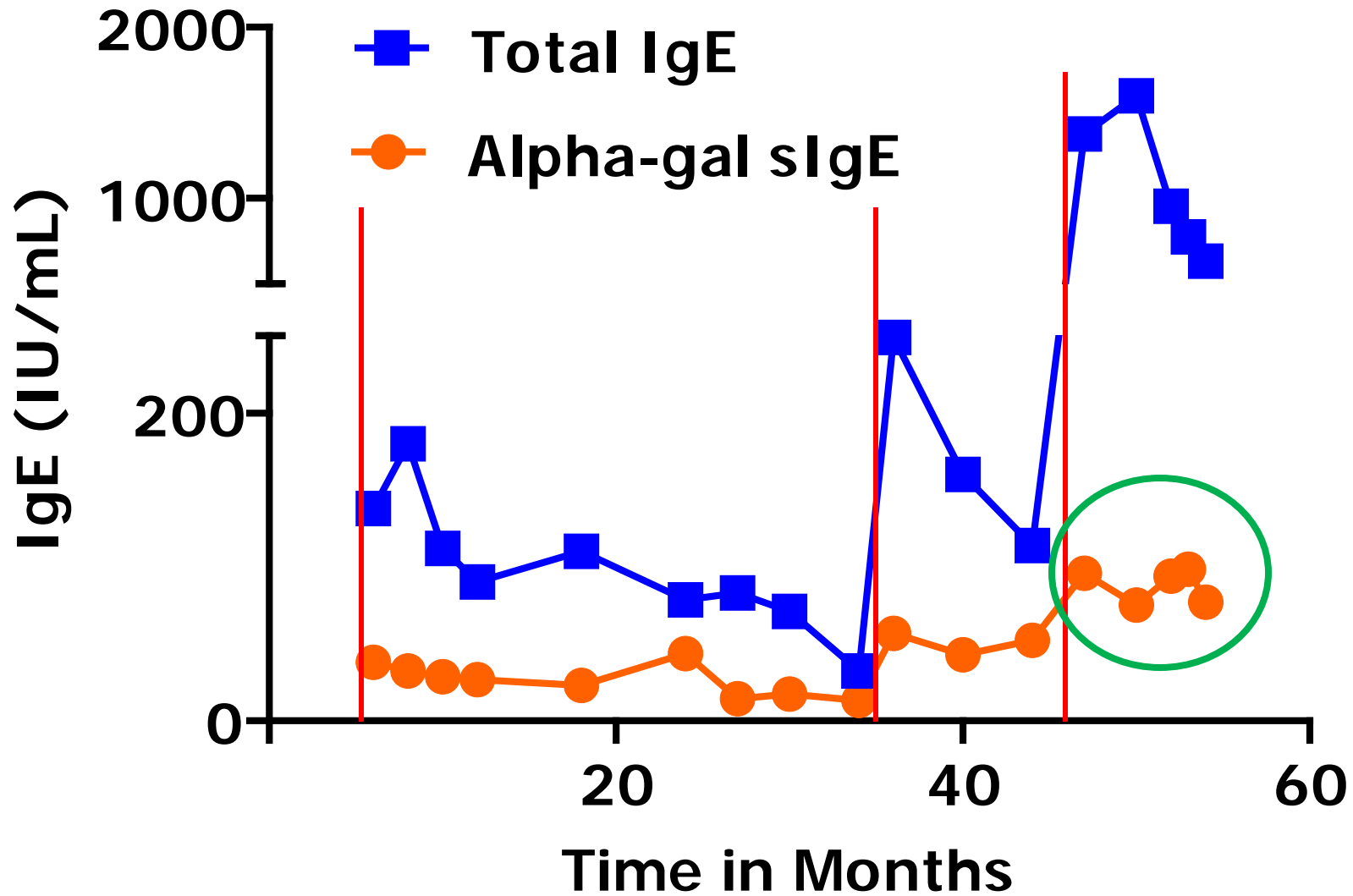
IgE to Alpha-gal and Total IgE Rise Following Tick Bites



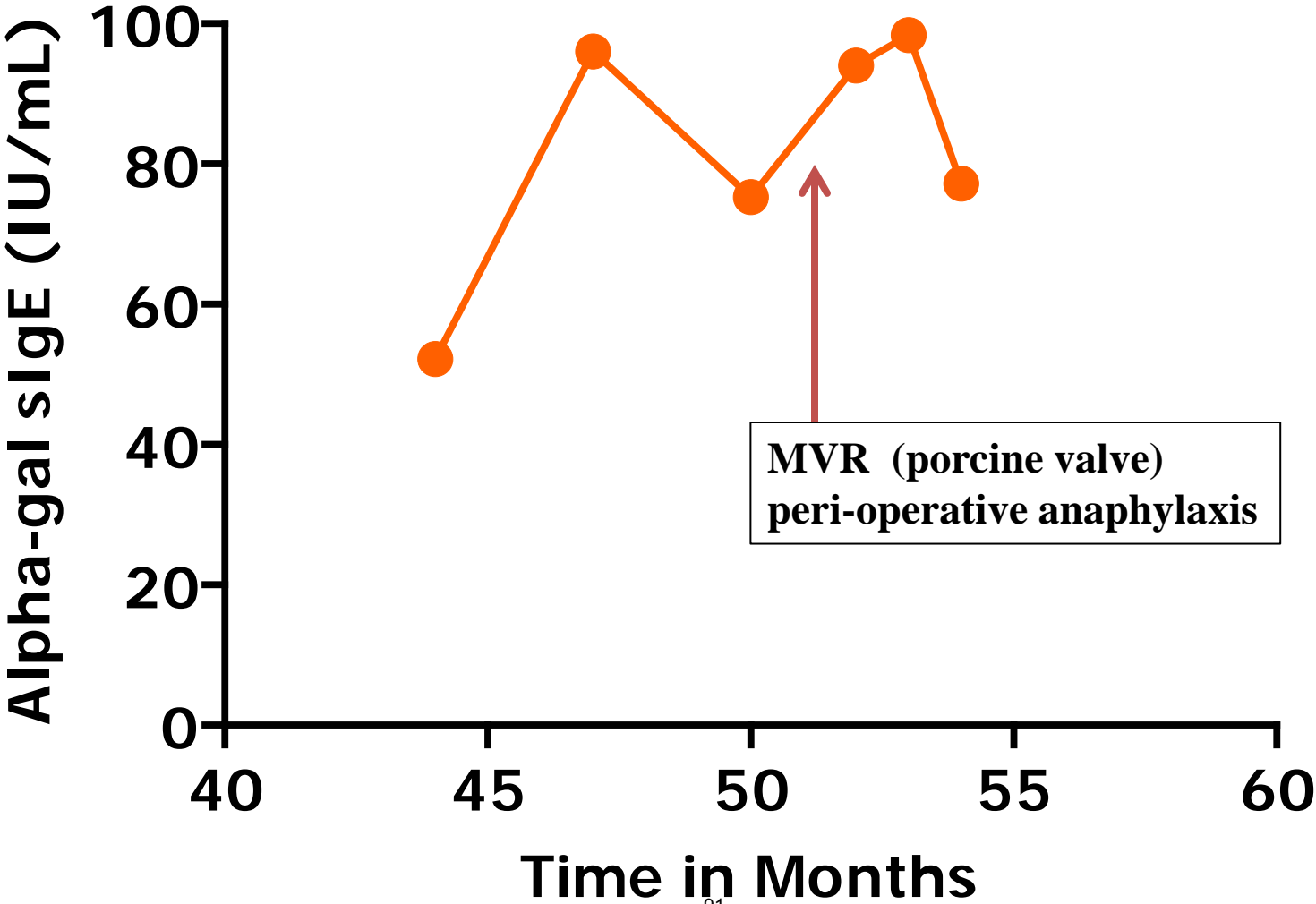
Tracking IgE to Alpha-gal and Total IgE over Time (E202)



Tracking IgE to Alpha-gal and Total IgE over Time (E202)



Tracking IgE to Alpha-gal and Total IgE over Time (E202)



Gelatin content of vaccines licensed in the United States, 2008 ‡

Vaccine	Trade Name	Quantity *(per dose)
DTaP	Tripedia	0.0015 mg
Influenza	Fluzone	≤0.025 mg
	Flumist	2 mg
Measles, mumps, Rubella	MMR II	14.5 mg
Varicella	Varivax	12.5 mg
Shingles	Zostavax	15.58 mg
Rabies	Rabavert	<12 mg

*All gelatin contained in vaccines is porcine in origin.

‡The Children's Hospital of Philadelphia, Vaccine Education Center

MANAGEMENT

- Avoidance diet:
 - *Mammalian meat, esp fatty cuts (ice cream)*
 - *Dairy and cheese usually tolerated*
 - *Few issues with gelatin*
- Caution re: exercise, alcohol, recent tick bites
- Monitor IgE to alpha-gal over time
 - *Pork sausage (3) challenge when level declines signif.*
- Counsel re: bioprosthesis (valve, ligaments, etc) and vaccines (Zostavax, ?MMR)

SUMMARY

- Evidence suggests that tick bites can affect total and specific IgE levels in some patients
- In many cases, the sensitization to alpha-gal appears to decrease over time
- Additional tick bites may lead to more significant increases in the IgE response
- Initial report that galactose-alpha-1,3-galactose may exist in the GI tract of *Ixodes ricinus*

Galactose- α -1,3-galactose and Delayed Anaphylaxis, Angioedema, and Urticaria in Children

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KEY WORDS

α -Gal, galactose- α -1,3-galactose, delayed anaphylaxis, pediatric urticaria

ABBREVIATIONS

α -Gal—galactose- α -1,3-galactose

Ig—immunoglobulin

Dr Kennedy performed data analysis and patient enrollment, and drafted the manuscript; Drs Stallings, Lane, and Matos were instrumental in patient enrollment; Dr Platts-Mills conceptualized and designed the study, and was involved in drafting the manuscript; Mr Oliveira performed specific immunoglobulin E (IgE) measurements; Ms Workman collected and performed all specific IgE measurements; Ms James performed data analysis and assisted in the specific IgE measurements; Dr Tripathi helped with the draft of the manuscript; Dr Heymann was involved in enrolling patients as well as in drafting the manuscript; Dr Commins conceptualized and designed the study, and was instrumental in patient enrollment, data analysis, and drafting the manuscript; and all authors approved the final manuscript as written.

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FINANCIAL DISCLOSURE: Dr Platts-Mills is a consultant to Viracor/IBT and has a patent on the use of streptavidin solid phase to evaluate immunoglobulin E antibodies to recombinant molecules; Dr Lane is a consultant for Mylan Specialty, which markets the EpiPen epinephrine autoinjector, used for life-threatening anaphylaxis/food allergy; the other authors have indicated they have no financial relationships relevant to this article to disclose.

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WHAT'S KNOWN ON THIS SUBJECT: Delayed anaphylaxis, urticaria, and angioedema to mammalian meat products were first described in the adult population in 2009. Patients with this syndrome who consume mammalian meat typically develop symptoms 4 to 6 hours after ingestion.



WHAT THIS STUDY ADDS: Specific diagnoses for children who develop urticaria, angioedema, and idiopathic anaphylaxis are few and far between. We have now shown delayed anaphylaxis, urticaria, and angioedema due to mammalian meat products in the pediatric population.

abstract



BACKGROUND AND OBJECTIVE: Despite a thorough history and comprehensive testing, many children who present with recurrent symptoms consistent with allergic reactions elude diagnosis. Recent research has identified a novel cause for “idiopathic” allergic reactions; immunoglobulin E (IgE) antibody specific for the carbohydrate galactose- α -1,3-galactose (α -Gal) has been associated with delayed urticaria and anaphylaxis that occurs 3 to 6 hours after eating beef, pork, or lamb. We sought to determine whether IgE antibody to α -Gal was present in sera of pediatric patients who reported idiopathic anaphylaxis or urticaria.

METHODS: Patients aged 4 to 17 were enrolled in an institutional review board–approved protocol at the University of Virginia and private practice allergy offices in Lynchburg, VA. Sera was obtained and analyzed by ImmunoCAP for total IgE and specific IgE to α -Gal, beef, pork, cat epithelium and dander, Fel d 1, dog dander, and milk.

RESULTS: Forty-five pediatric patients were identified who had both clinical histories supporting delayed anaphylaxis or urticaria to mammalian meat and IgE antibody specific for α -Gal. In addition, most of these cases had a history of tick bites within the past year, which itched and persisted.

CONCLUSIONS: A novel form of anaphylaxis and urticaria that occurs 3 to 6 hours after eating mammalian meat is not uncommon among children in our area. Identification of these cases may not be straightforward and diagnosis is best confirmed by specific testing, which should certainly be considered for children living in the area where the Lone Star tick is common. *Pediatrics* 2013;131:e1545–e1552

In studies in which the etiology of anaphylaxis has been established, foods or venoms cause most reactions,¹ and, classically, these immunoglobulin E (IgE)-mediated reactions are thought to occur within 5 to 30 minutes after ingestion or injection of an offending agent.² Numerous epitopes responsible for IgE-mediated food allergy have been described and are primarily protein-based. Although it is well known that the carbohydrate moieties present on many plant foods can induce antiglycan IgE responses, the clinical significance of these cross-reactive carbohydrate determinants is unclear.^{3–5} In contrast, recent work has shown that IgE antibodies specific for the carbohydrate, galactose- α -1,3-galactose (α -Gal), are capable of eliciting serious, even fatal, delayed reactions that occur 3 or more hours after eating red meat.^{6,7}

An IgG/IgM immune response to α -Gal has been well described, and this mediates hyperacute rejection of pig-to-primate xenotransplantation.⁸ Work by Chung et al⁹ demonstrated that in adults, an IgE response to α -Gal was responsible for immediate hypersensitivity reactions that occurred during infusion of the monoclonal antibody cetuximab, an anti-epidermal growth factor receptor cancer therapeutic. The α -Gal carbohydrate moiety is known to be present on multiple tissues (notably thyroglobulin) from nonprimate mammals,^{10,11} and more recently, IgE to α -Gal has been associated with delayed urticaria and even anaphylaxis.^{6,7} The development of IgE antibody to α -Gal has been linked to bites from ecto-parasitic ticks, especially those of the Lone Star tick, *Amblyomma americanum*.¹² Patients with IgE antibody to α -Gal report symptoms of urticaria, angioedema, or even anaphylaxis starting 3 to 6 hours after the ingestion of mammalian meat products.⁷ The symptoms can be severe,

and many patients have required epinephrine injections for their reactions as well as care in emergency departments.^{7,13} Because the timing of ingestion occurs much earlier than the actual symptoms, diagnosis and recognition of this food allergy has been challenging. In fact, we have seen many children who had been diagnosed with idiopathic urticaria/anaphylaxis, or who had been specifically told that the reactions were not a result of food allergy, who had IgE antibodies to α -Gal and, in retrospect, a history consistent with delayed reactions to mammalian meat (A.P.S., P.W.H., S.P.C., unpublished observations). Immediate hypersensitivity to meat in children has been reported by multiple investigators^{14–18} and the role of beef allergens in children with atopic dermatitis and milk sensitization has also been well established.^{19,20}

Because α -Gal has been found to be an important cause of urticaria, angioedema, and anaphylaxis in the adult population, we investigated whether IgE antibodies to α -Gal were present in the sera of pediatric patients with a clinical history suggestive of delayed urticaria, angioedema, or anaphylaxis to mammalian meat products. Here we report 45 pediatric patients, aged 4 to 17, who were found to have IgE antibodies to α -Gal. To our knowledge, this is the first report of delayed reactions to mammalian meat in the pediatric population.

METHODS

Patients and Control Subjects

The University of Virginia Human Investigation Committee has approved these studies. Our patients were enrolled as subjects from the University of Virginia Allergy and Immunology Clinic, as well as from private practice allergy clinics in Lynchburg, VA, because each had a history suggestive of delayed anaphylaxis, urticaria, or angioedema.

A total of 51 subjects were enrolled from September 2011 to May 2012 on the basis of clinical history and answers to questions regarding tick bites and bite site characteristics. Specific questions included (1) did episodes occur before or after midnight, (2) did episodes follow having eaten mammalian meat at the meal before the reaction (even if 4 to 5 hours prior), and (3) was there a history of tick or seed tick bites. Additional subjects aged 4 to 18 were enrolled ($n = 142$) from the University of Virginia Hospital where they presented with (or without) wheeze.²¹

ImmunoCAP IgE Assays

Total and specific IgE antibodies were measured by using either commercially available ImmunoCAP (Phadia US, Portage, MI) or a modification of the assay with streptavidin on the solid phase (α -Gal, Fel d 1).^{7,22} The assays were performed with the ImmunoCAP 250 instrument and the results expressed as IU/mL. For specific assays, the cutoff used for a positive reaction was 0.35 IU/mL. The sera were tested with commercially available assays for IgE antibodies to dust mite (*Dermatophagoides pteronyssinus*), cat (dander and epithelium in addition to Fel d 1), dog dander, Timothy grass, *Alternaria alternata*, oak, beef, pork, chicken, codfish, cow's milk and milk components (Bos d 4, Bos d 5, Bos d 8), boiled milk, goat's milk, peanut, egg, and total IgE.

Statistical Analysis

We compared the specific IgE antibody results between α -Gal, beef, and pork to fish, chicken, peanut, and egg by using the Mann-Whitney test. We correlated quantitative measures of IgE antibodies between α -Gal and other specific IgE antibodies by using the Spearman rank-order correlation. A $P < .05$ was considered to indicate statistical significance. Statistical

analyses were performed with GraphPad Prism 6.0 (GraphPad Software, La Jolla, CA).

RESULTS

Our population included children ($n = 51$) with a history of recurrent urticaria, idiopathic anaphylaxis, or angioedema suggestive of a delayed response to mammalian meat, of which 45 tested positive for IgE antibody to α -Gal (Table 1). Some patients were referred as cases of chronic urticaria; however, on careful questioning, a more appropriate diagnosis would have been acute, recurrent urticaria. Many of the patients had used an emergency department for their symptoms (5/51 had been to the emergency department ≥ 4 times before diagnosis), and they required the use of epinephrine, antihistamines, and/or injected steroids. There were also several patients who had required admission to the hospital for observation (Table 1). All of these patients had a clear history of tick exposure before our evaluation of IgE to α -Gal, and 39 had histories of itching, redness, and swelling for several weeks after the tick bite (Table 1). Of the 51 children, 6 subjects were enrolled with similar histories, yet were found to be negative for IgE antibody to α -Gal.

As previously reported in adults, our pediatric subjects had positive immunoassays to mammalian meat products, including beef and pork (Fig 1). The specific IgE levels for these tests were significantly higher than those for fish ($P < .05$), chicken ($P < .001$), egg ($P < .05$), and peanut ($P < .001$) by Mann-Whitney analysis. There was a close correlation ($r = 0.99$) between beef- and pork-specific IgE, supporting the view that these assays were measuring IgE antibodies to a single component: α -Gal (Fig 2A). There was also a strong correlation between a positive immunoassay for α -Gal and a positive

TABLE 1 Patient Demographics

	$n = 51$
Gender, % male	69
Mean age at presentation (range)	12 (4–17)
Total IgE, geometric mean (95% confidence interval)	147 IU/mL (105–206 IU/mL)
No. of subjects testing positive for IgE antibody to α -Gal (%)	45 (88)
Symptoms at presentation, %	
Anaphylaxis ^a	44
Gastrointestinal/Oral	64
Urticaria	92
Angioedema	31
Average time to symptoms (range)	4.68 h (10 min to 24 h)
Tick exposure, %	100
Redness and itching at site of tick bite	87
Tick-borne illness ^b	10
Emergency department visits, %	46 ^c
Medications administered in the emergency department, %	
Epinephrine	19
Antihistamines	35
Oral steroids	19
Parenteral steroids	17
Intravenous fluids	17
Hospital admissions, %	8

^a Anaphylaxis was defined as hypotension and/or respiratory symptoms including laryngeal edema and wheezing.

^b All patients with positive answers reported a history of Lyme disease.

^c Five of the 45 subjects required ≥ 4 visits to the emergency department for symptoms.

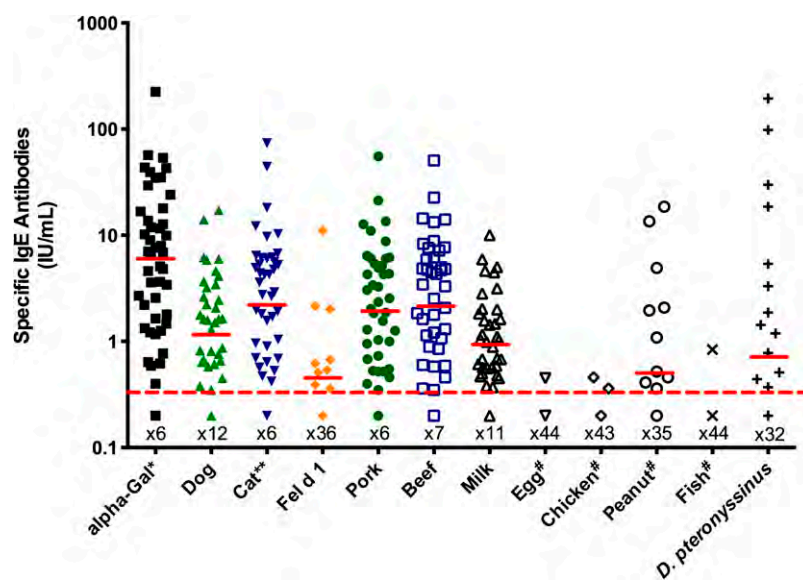


FIGURE 1

Specific IgE antibody binding to allergens in serum samples from 45 patients with IgE antibodies to α -Gal. The horizontal lines indicate geometric mean values. Numbers below the limit of detection indicate the number of negative values for each allergen. * Complete panel of immunoassays was performed for those sera positive for IgE antibody to α -Gal ($n = 45$). ** Cat allergen includes epithelium and dander. # The values for chicken, egg, peanut, and fish have significantly lower titers ($P < .05$) compared with α -Gal, beef, and pork by means of a Mann-Whitney analysis.

test for beef and pork ($r = 0.87$ and $r = 0.89$, respectively; Table 2, Fig 2 B and C). The symptoms reported by these children included urticaria, angioedema, and anaphylaxis, and in nearly

every case these symptoms were delayed 3 to 6 hours, much like those of their adult counterparts (Table 1). Milk-specific IgE was also elevated in these patients, as reported in previous

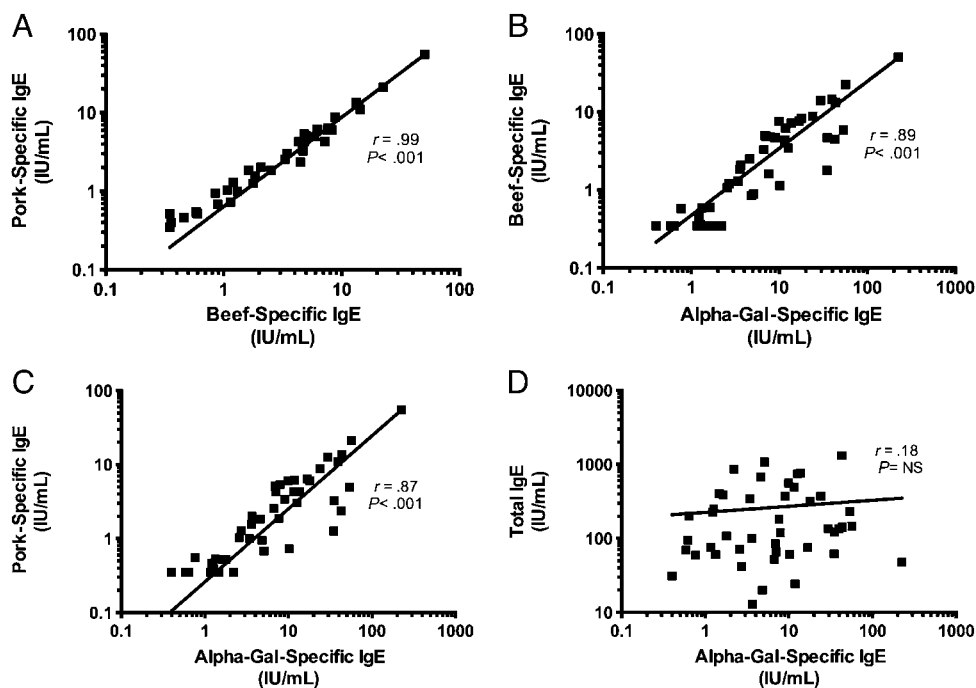


FIGURE 2

Correlations of IgE to α -Gal and specific allergens. A, Correlation of IgE antibody to pork and IgE antibody to beef ($r = 0.99$), suggesting that these tests are actually measuring the amount of specific IgE to α -Gal in the serum. B, Correlation of IgE antibody to α -Gal and beef ($r = 0.89$; $P < .001$) in patients with IgE antibody to α -Gal. C, Correlation of IgE antibody to α -Gal and pork ($r = 0.87$; $P < .001$) in patients with IgE antibody to α -Gal. D, Correlation of IgE antibody to α -Gal and total IgE ($r = 0.18$; $P =$ not significant) in patients with IgE antibody to α -Gal.

studies.⁷ However, tests for IgE to milk components, including α -lactalbumin (Bos d 4), β -lactoglobulin (Bos d 5), and casein (Bos d 8), were negative in most of the patients who had a positive immunoassay to milk. Boiled milk immunoassays were also negative in this same population (Fig 3). To confirm that α -Gal–specific IgE antibody were responsible for the positive cow's milk IgE test, absorption studies were carried out on 3 sera, which showed that removing IgE antibody to α -Gal also removed the positive milk IgE result (Supplemental Table 3).

In keeping with the known distribution of α -Gal, positive immunoassay responses were seen to cat dander and epithelium and dog dander in our patients with α -Gal allergy (Fig 1). Despite a positive test for cat and dog, only 9 of 32 subjects reported rhinitis symptoms on exposure to cat or dog. The immunoassay test for these mammals is known to contain α -Gal

because of the presence of proteins, such as cat IgA (Fel d 5).²³ Sensitization to dust mite and to the major cat allergen (Fel d 1) were similar to the general population (Fig 1) and are not associated with the α -Gal syndrome.

To further characterize the IgE antibody to α -Gal response in the pediatric population, an assessment of the prevalence of this antibody response in a geographically similar but distinct cohort was performed. Sera from subjects ($n = 142$) presenting to the University of Virginia Hospital with and without wheeze were assayed for indoor, outdoor, and food-specific IgE antibody responses (Fig 4A). In this group of 142 subjects, the percentage of sera positive for IgE antibody to α -Gal overall was 24%. Because this cohort was enrolled to investigate asthma, it included patients with and without wheezing.²¹ As might be expected, patients with wheezing (surrogate for asthma) had higher

overall IgE percent positive for many allergens but notably percent α -Gal sensitization was not significantly different between wheezing and non-wheezing subjects ($P = .43$; Fig 4 A and B). Analysis of the 3 different cohorts showed that the IgE antibody titer to α -Gal was significantly higher in patients reporting delayed reactions after consuming mammalian meat as compared with those subjects enrolled with and without wheeze ($P < .001$; Fig 4B). A more detailed analysis of the IgE antibody to α -Gal response shows that among those subjects with wheeze, IgE to α -Gal comprised $<1\%$ of the total IgE in most cases (Supplemental Fig 5). On the contrary, those subjects enrolled specifically because the clinical history supported delayed reactions to mammalian meat had IgE to α -Gal responses that constituted $>1\%$ of total IgE, and in many instances $>5\%$ of total IgE (Supplemental Fig 5).

TABLE 2 Correlations Between the IgE Specific for α -Gal (IU/mL) and Other Specific Allergens (IU/mL)

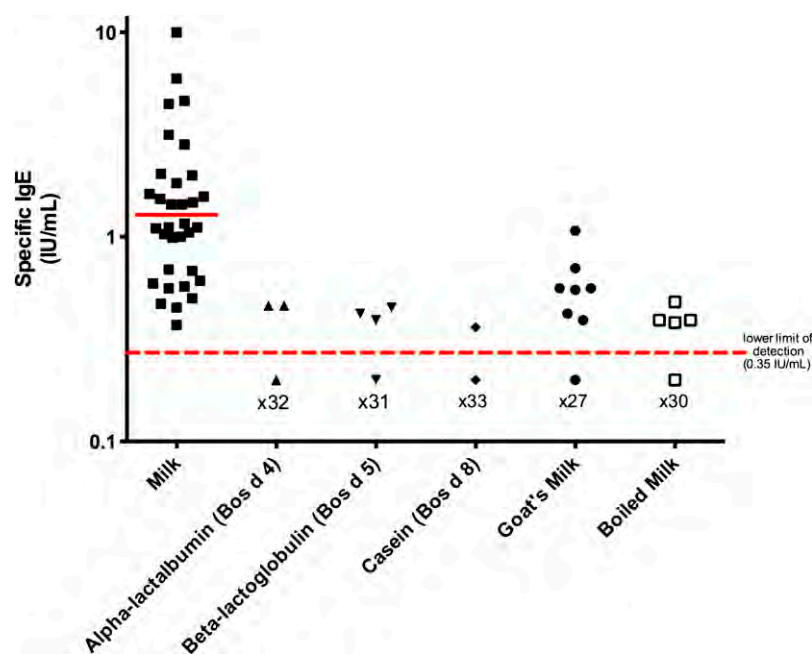
Specific IgE Antibody	No. of Positives/No. Tested	Spearman Correlation (<i>r</i>) With α -Gal	<i>P</i> Value
α -Gal	45/45	1	
Dog dander	33/45	0.71	<.001
Cat ^a	39/45	0.73	<.001
Fel d 1 ^b	9/45	0.07	.66
Pork ^c	39/45	0.87	<.001
Beef ^c	38/45	0.89	<.001
Milk	34/45	0.79	<.001
Peanut	10/45	-0.07	.67
Dust mite ^d	13/45	0.25	.1

^a Cat immunoassay includes epithelium and dander.

^b Fel d 1 is the major cat allergen.

^c Pork- and beef-specific IgE antibody were significantly correlated with each other ($r = 0.99$ and $P < .001$).

^d Dust mite = *D pteronyssinus* immunoassay.

**FIGURE 3**

Component analysis of milk-allergic children with α -Gal. Patients with α -Gal-specific IgE who were positive for specific IgE to milk ($n = 34$) were tested for milk components, including α -lactalbumin, β -lactoglobulin, and casein-specific IgE. Interestingly, there does not appear to be any reactivity to the milk components (α -lactalbumin, β -lactoglobulin, and casein), suggesting that there is no α -Gal in these immunoassays. Similar results are present for boiled milk and goat's milk.

DISCUSSION

The α -Gal syndrome, in children and adults, is unlike any other known IgE-mediated food allergy. Despite high titers of IgE antibodies to beef and pork, these cases consistently report a delay of 3 to 6 hours after eating mammalian meat.⁷ Furthermore, the symptoms often become severe, including significant episodes of hives

and hypotension. In fact, >45% of the subjects used an emergency department at least once for their symptoms and 8% required admission to the hospital for observation (Table 1). Thus, it is our general practice to prescribe an epinephrine autoinjector and instruct patients in its proper use. Not only the serious nature of the reactions but also the rising frequency of idiopathic angioedema and urticaria

across all age groups^{24–29} underscore the importance of identifying a cause for these cases if possible. Our results show clearly that physicians should keep this diagnosis in mind even in the pediatric population, especially if the history is consistent with the disease syndrome, including delayed symptoms after ingestion of beef, pork, lamb, or even milk.

It is important to note, however, that patients with IgE antibody to α -Gal may not experience reactions with every ingestion of mammalian meat. The explanations for such an observation are several-fold. First, α -Gal is a carbohydrate and this “inconsistency” may simply be a result of the inherent properties of digestion, processing, and absorption of glycans. Second, the amount of α -Gal that actually reaches the bloodstream in an antigenic form (which we believe to be that of a glycolipid) may be significantly less than is ingested. Moreover, the food itself (ie, hamburger versus cow's milk) may offer more or less antigen. Fourth, the dose of meat appears to be important, and in some instances children are able to consume a small amount of mammalian meat or products without adverse reactions. Fifth, it may well be that preparation (mechanical, thermal, or freezing) is a significant factor in contributing to whether foods retain enough of the appropriate antigen to cause a reaction. Finally, it is also important to keep in mind that the natural history of this IgE antibody response appears to be one that decreases over time. Thus, as the IgE antibody titer decreases, children could experience fewer or inconsistent reactions.

The incidence of food allergy is increasing across the population, with almost 6% of children and 4% of adults in North America now allergic to 1 or more foods.^{30,31} Children who develop IgE antibody to α -Gal may have positive skin, intradermal, or immunoassay

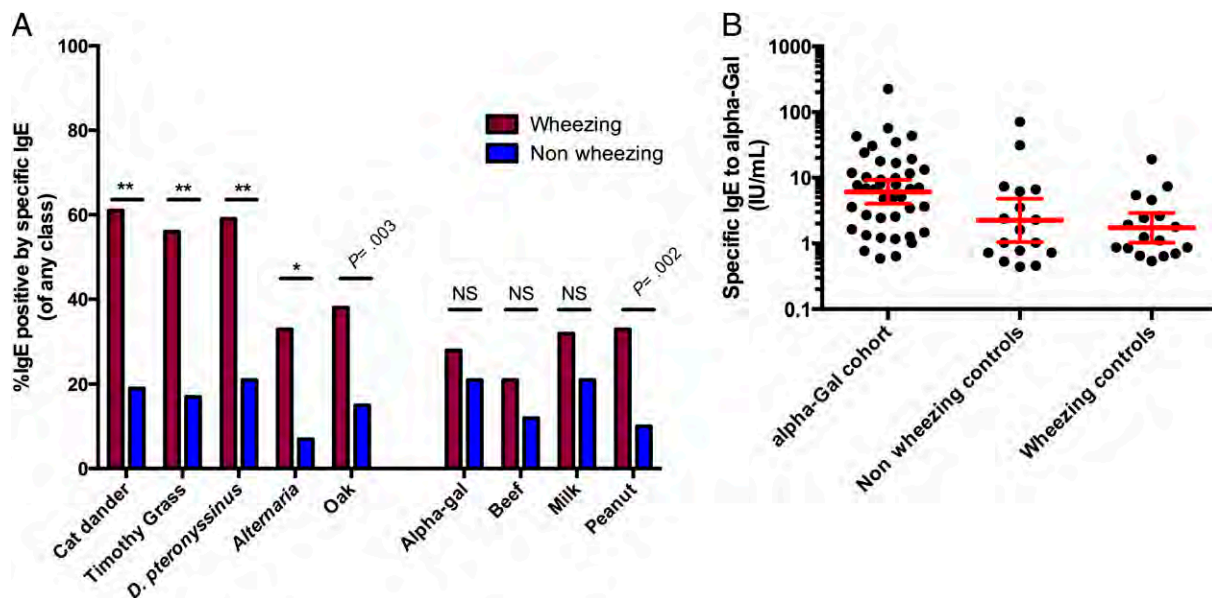


FIGURE 4

A, Percentage of children (aged 4–18) positive for specific IgE antibodies in wheezing ($n = 61$; red) and nonwheezing ($n = 81$; blue) control groups. There were significant differences between the wheezing and control population with regard to aeroallergen sensitization (** $P < .001$; * $P = .001$), whereas there were no differences in sensitization patterns to α -Gal, beef, or milk ($P = .43$, $P = .15$, and $P = .21$, respectively). B, Comparison of positive tests for α -Gal among an age-matched pediatric cohort with symptoms of delayed mammalian meat allergy ($n = 45$) and a cohort of wheezing ($n = 17$) and nonwheezing ($n = 16$) control subjects in the hospital. The pediatric cohort with symptoms of delayed mammalian meat allergy has significantly higher levels of specific IgE to α -Gal ($P < .001$). NS, not significant.

testing to milk, beef, pork, cat, or dog.³² It is important to understand that many children suffer from milk allergy, but IgE to α -Gal is distinct from the more traditional, protein-based cow's milk allergy. α -Gal–related reactions present in older children, many of whom have no previous history of either food allergy or any allergic disease.⁷ Clinicians should recognize that the carbohydrate moiety α -Gal is found in mammalian milk, as evidenced by the positive immunoassay results to cow's milk and goat's milk. Therefore, in a patient older than 5 who has an apparent new-onset milk allergy, IgE antibody to α -Gal should be considered as an alternative diagnosis to a protein-based milk allergy, a cross-reactivity between beef allergy and cow's milk,¹⁹ or even a distinct mammalian protein cross-reactivity.¹⁸

Interestingly, we were unable to show positive tests for α -Gal on the individual components of milk as tested in this study. Children with IgE antibody to

α -Gal (and, therefore, “milk allergic”) had negative immunoassays to α -lactalbumin, β -lactoglobulin, and casein in 32, 31, and 33 of 34 instances, respectively, leading us to surmise that these milk protein antigens are not significant sites of α -Gal–based glycosylation. Similarly, one might anticipate that the allergens bovine immunoglobulin (Bos d 7) or bovine serum albumin (Bos d 6) could contain glycosylation with α -Gal, but the published evidence that has assessed this possibility for Bos d 6 suggests α -Gal is not present, and our unpublished data have also been in keeping with a lack of α -Gal on bovine serum albumin.¹¹ The negative results for milk allergens could also be explained by the processing of these components for the immunoassay, which might change the structure or alter the galactose linkages. The latter theory is supported by our finding that the boiled milk immunoassay was negative in most of the patients with a positive α -Gal–specific

IgE, whereas another mammalian milk (goat) was positive in those sera that had the highest titer of IgE antibody to cow's milk. Taken together, the data suggest that the goat's milk ImmunoCAP has fewer α -Gal epitopes than does the cow's milk assay, not that α -Gal is absent from goat's milk or that goat's milk may be a safe alternative for these children. In fact, we have not a priori recommended removal of milk or dairy products from the diet of adults with this syndrome if they have previously tolerated these products. We have continued a similar approach in the pediatric population, unless the allergic episodes persist, at which time we would suggest performing an oral milk challenge.

Skin testing for beef, pork, or lamb (mammalian meat) in both adult and pediatric patients has been challenging. Many patients have only small reactions (2–5 mm) to these allergens by skin-prick testing, and intradermal

tests have been used in adults to clarify the intermediate results.⁷ We have, on occasion, also performed intradermal testing in older teenagers, and these results mirrored those seen in adults. Overall, we are less likely to perform intradermal testing in children and, therefore, recommend use of in vitro assays. Although we have performed mammalian meat challenges in adult subjects to document the delayed appearance of clinical symptoms, these food challenges have produced significant symptoms beyond what the subject had reported after natural exposure. In protein-based food allergies in which symptoms arise in 5 to 30 minutes, food challenges use small amounts of allergen and proceed incrementally, such that the procedure is stopped when patients begin to react. Because of the time course to symptoms, incremental dosing is not possible in the case of delayed reactions to mammalian meat and the entire dose must be given at the start of the challenge. Because of the (significant) reactions observed during mammalian meat challenges with adult subjects and the inability to incrementally dose, we do not plan to perform food challenges in pediatric subjects and acknowledge the lack of food challenges as a limitation in our study.

The pediatric population seems to follow the trend seen in adult subjects with regard to the geographic distribution of this disease. Screening serum samples from multiple geographic

locales reveals a distinct regional pattern of disease in the southeastern United States, a pattern that roughly correlates with the higher incidence of cetuximab hypersensitivity in adults.³³ In fact, we have been made aware of children presenting with IgE antibody to α -Gal in numerous centers throughout the eastern and now central United States. Colleagues at Duke University (Dr Michael Land and Dr Moira Breslin), Kansas City Children's (Dr Paul Dowling and Dr Tara Federly), and in East Hampton, NY (Dr Erin McGintee) have diagnosed pediatric patients with IgE antibody to α -Gal and the characteristic delayed reactions to mammalian meat. Based on our assessment of sera from children enrolled in studies in central Virginia, the prevalence of specific IgE (sIgE) antibody to α -Gal can be as high as 15% in some areas. Interestingly, this area overlaps with the known distribution of the Lone Star tick, *A americanum*.³⁴ As suggested in our recent publication, we believe that there is a causal relationship between tick bites and sensitization to α -Gal.¹² In the current study, >90% of patients with this syndrome reported tick bites in the previous year. For patients with IgE antibody to α -Gal, tick bites cause significantly pruritic reactions at the site of the bite(s) which often persist. Thus, 2 clinically relevant questions that can assist in formulating a diagnosis are to inquire about a history of tick or seed tick bites, and further, whether the site(s) of a bite(s) had persistent (ie, 2–3 weeks) itching, erythema, or swelling.¹²

Of note, in our experience, if patients are able to avoid subsequent tick bites, the level of α -Gal-specific IgE tends to decrease over time. In fact, some adult patients with this form of allergy have been able to tolerate mammalian meat again after avoiding additional tick bites for 1 to 2 years (S.P.C., T.A.E.P-M., and J.L.K., unpublished data, 2010–2013).

Although there are multiple potential causes for both acute and chronic urticaria, as well as angioedema and idiopathic anaphylaxis, we report here 45 pediatric patients who fit the syndrome of delayed reactions to red meat. This study not only further broadens the differential for evaluating "idiopathic" allergic reactions but informs of an expanded population at risk for developing this unique allergy. In keeping with the known distribution of α -Gal, we have found that restriction of mammalian meat can lead to complete remission of previous symptoms. Most children and adults are able to continue to drink milk products, although a few patients may have symptoms with dairy ingestion. Importantly, we believe that this research provides clear evidence that the α -Gal syndrome is important in the pediatric population, and it should be diagnostically considered in children with a history suggestive of delayed responses to red meat and acute, recurrent urticaria, angioedema, or idiopathic anaphylaxis, particularly in those patients living in areas where the Lone Star tick is common.

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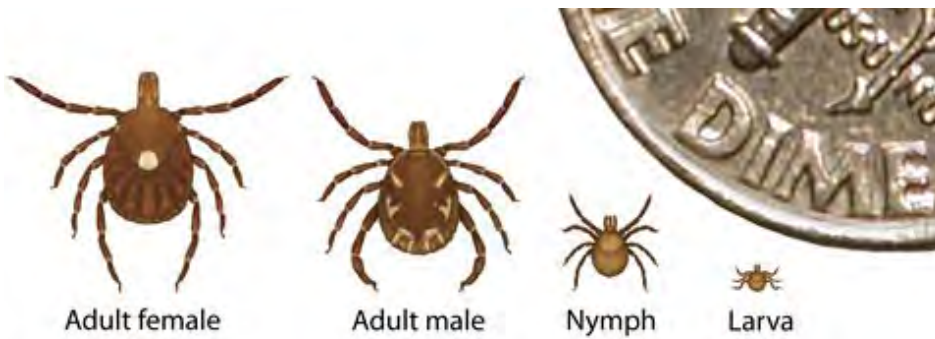


STARI or Lyme?

Lone star tick a concern, but not for Lyme disease

Many people, even health care providers, can be confused about whether the lone star tick causes Lyme disease. It does not. Patients bitten by lone star ticks will occasionally develop a circular rash similar to the rash of early Lyme disease. The cause of this rash has not been determined; however, studies have shown that the rash is not caused by *Borrelia burgdorferi*, the bacterium that causes Lyme disease.

This condition has been named southern tick-associated rash illness (STARI). The rash may sometimes be accompanied by fatigue, headache, fever, and muscle pains. In the cases of STARI studied to date, the rash and accompanying symptoms have resolved following treatment with an oral antibiotic (doxycycline), but it is unknown whether this medication speeds recovery. STARI has not been linked to arthritis, neurologic disease, or chronic symptoms. Researchers once hypothesized that STARI was caused by the spirochete, *Borrelia lonestari*, however further research did not support this idea (<http://cid.oxfordjournals.org/content/40/3/423.full>). The cause of STARI remains unknown.



Lone star ticks have not been shown to transmit *Borrelia burgdorferi*, the cause of Lyme disease. In fact, their saliva has been shown to kill *Borrelia* (Ledin et al., 2005, Zeidner et al., 2009).

The lone star tick, *Amblyomma americanum*, is found throughout the eastern, southeastern and south-central states. The distribution, range and abundance of the lone star tick have increased over the past 20-30 years, and lone star ticks have been recorded in large numbers as far north as Maine and as far west as central Texas and Oklahoma. All three life stages (larva, nymph, adult) of the lone star tick will feed on humans, and may be quite aggressive. Lone star ticks will also feed readily on other animals, including dogs and cats, and may be brought into the home on pets. The saliva from lone star ticks can be irritating; redness and discomfort at a bite site does not necessarily indicate an infection.

People should monitor their health closely after any tick bite, and should consult their physician if they experience a rash, fever, headache, joint or muscle pains, or swollen lymph nodes within 30 days of a tick bite. These can be signs of a number of [tickborne diseases](#).

Tick-borne illness may be prevented by avoiding tick habitat (dense woods and brushy areas), using insect repellents containing DEET or permethrin, wearing long pants and socks, and performing tick checks and promptly removing ticks after outdoor activity. [Additional prevention tips](#) are available.

Study results: Distinctions between STARI and Lyme disease symptoms

In a study that compared physical findings from STARI patients in Missouri with Lyme disease patients in New York (Wormser et al, 2005), several key differences were noted:

- Patients with STARI were more likely to recall a tick bite than were patients with Lyme disease.
- The time period from tick bite to onset of the skin lesion was shorter among patients with STARI (6 days, on average).
- STARI patients with an erythema migrans rash were less likely to have other symptoms than were Lyme disease patients with erythema migrans rash.
- STARI patients were less likely to have multiple skin lesions, had lesions that were smaller in size than Lyme disease patients (6-10 cm for STARI vs. 6-28 cm for Lyme disease), and had lesions that were more circular in shape and with more central clearing.
- After antibiotic treatment, STARI patients recovered more rapidly than did Lyme disease patients.

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Content source: Centers for Disease Control and Prevention (<http://www.cdc.gov/>)

National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) (<http://www.cdc.gov/ncezid>)

Division of Vector-Borne Diseases (DVBD) (<http://www.cdc.gov/ncezid/dvbd/index.html>)

common name: lone star tick

scientific name: *Amblyomma americanum* (Linnaeus) (Acari: Ixodidae)

[Introduction](#) - [Synonymy](#) - [Distribution](#) - [Description and Life Cycle](#) - [Hosts](#) - [Medical and Veterinary Importance](#) - [Management](#) - [Selected References](#)

Introduction ([Back to Top](#))

The lone star tick, *Amblyomma americanum*, was first described by Linnaeus in 1758. Lone star ticks feed on the blood of various animals (domesticated and wild) as well as humans. The tick was first considered a nuisance as it does not transmit the etiological agent of Lyme disease, but more recent studies have shown that this species can transmit various other pathogens to humans and other animals, such as those that cause ehrlichiosis, rickettsiosis, tularemia, and theileriosis.



Figure 1. Adult male (left) and female (right) lone star ticks, *Amblyomma americanum* (Linnaeus). Photographs by [Lyle Buss](#).

Synonymy ([Back to Top](#))

Acarus americanus Linnaeus, 1758
Acarus nigra De Geer, 1778
Rhynchoprion americanum Hermann, 1804
Ixodes nigra Latreille, 1804
Ixodes americanus Fabricius, 1805
Ixodes orbiculatus Say, 1821
Euthesius americanus Gistel, 1848
Ixodes unipunctata Packard, 1869
Ixodes unipictus Verrill, 1870
Amblyomma unipunctum Packard, 1870
Ixodes nigra Cobbold, 1879
Amblyomma foreli Stoll, 1890
Amblyomma unipunctatum Thurow, 1891

Ixodes unipuncta Lewis, 1899

Ixodes orbicularis Neumann, 1901

Amblyomma (Anastosiella) americanum Santos Dias, 1993

Amblyomma (Amblyomma) americanum Camicas et al., 1998

From the Catalogue of Life: 2009 Annual Checklist (ITIS 2013)

Distribution [\(Back to Top\)](#)

The lone star tick is widely distributed across the eastern, southeastern and midwestern U.S.A. (Fig. 2) (Childs and Paddock 2003). However, the tick may establish local populations outside of this range (Childs and Paddock 2003). The tick reportedly has been expanding its range north and west out of the historic range depicted in the distribution map provided by the CDC (Fig. 2) (Childs and Paddock 2003). The lone star tick typically is found in second growth woodland habitats that have populations of white-tailed deer (*Odocoileus virginianus*) (Kollars 1993).

With the re-introduction and increased populations of white-tailed deer in many areas of the eastern U.S.A., the ticks may further expand their range through transportation while feeding on white-tailed deer, a key host (Paddock and Yabsley 2007). Wild turkey populations also are a common host and may contribute to tick expansion by providing additional hosts for immature stages (Kollars et al. 2000). In some Midwestern states the lone star tick is colloquially known as the “turkey tick” due to its association with wild turkeys (Childs and Paddock 2003).

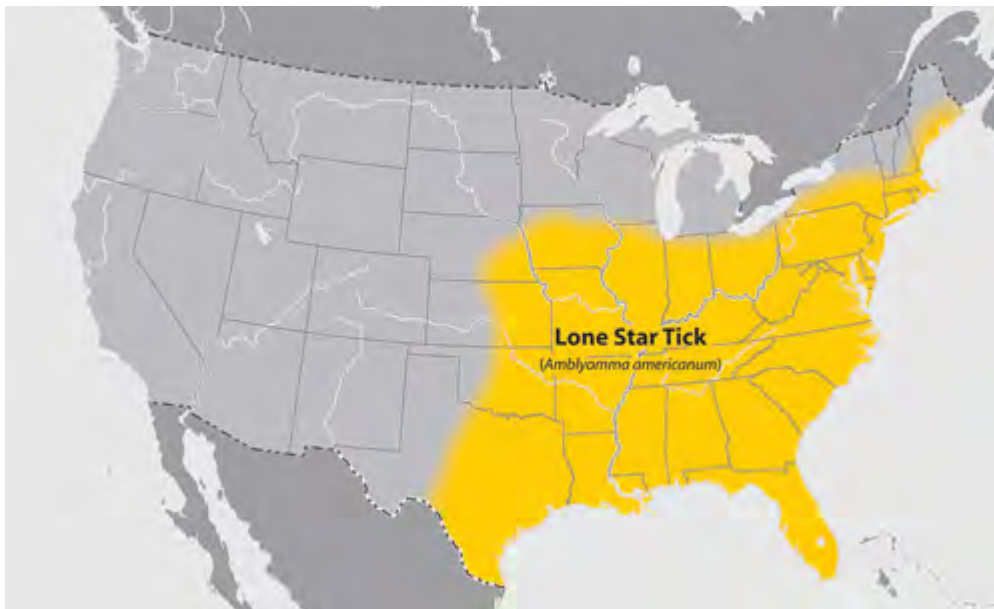


Figure 2. Distribution and range of the lone star tick, *Amblyomma americanum* (Linnaeus), in the United States. Image provided by the [Centers for Disease Control and Prevention](#).

Description and Life Cycle [\(Back to Top\)](#)

Adult lone star ticks are brown with eight legs and long mouthparts (Fig. 1). Lone star ticks are similar in body size when compared to other ticks like the American dog tick *Dermacentor variabilis* (Say), and the brown dog tick, *Rhipicephalus sanguineus* Latreille, but are larger than the blacklegged tick or deer tick, *Ixodes scapularis* Say. Adult lone star ticks exhibit sexual dimorphism: the female has a silvery-white spot near the center of her back on the posterior portion of the shield (scutum) and the male has varied white streaks or spots around the margins of the top of its body (Drees and Jackman 1999).

Lone star ticks are three-host ticks, feeding on different hosts during the larval, nymphal, and adult stages. The ticks have piercing-sucking mouthparts with chelicerae that pierce through the skin of the host. Attachment is facilitated by the tubular hypostome and a secreted cement- or latex-like compound that attaches ("glues") the tick to the host until feeding is complete (Adams et al. 2003). After feeding once in each larval, nymphal, and adult stage, the tick withdraws the mouthparts and drops to the ground to molt or oviposit, as described below.

A tick lifecycle begins when the blood-engorged female tick falls from the host and after several days deposits ~5,000 eggs on the soil in a "protected" location, such as in mulch or leaf litter (NCIPMI 1998). After dislodging from the host, the female will seek a microclimate, typically an area of high humidity at a soil level that is best suited for survival of the eggs (Patrick and Hair 1979). Females have been shown to search for a favorable microclimate up to 61 cm from where they were experimentally placed on the ground after feeding (Patrick and Hair 1979). Following an incubation period, larvae hatch from eggs and progress through a quiescent (resting) period, then seek a host by questing.

Questing is a behavior that entails climbing up an object, like a blade of grass, and waiting for a host to touch the larva. The larva then grasps the host and proceeds to move about the host, seeking a preferred feeding site. After acquiring a host, the larva attaches, blood-feeds for 1-3 days, detaches its mouthparts, and then drops from the host to digest its blood meal and molt into a nymph. Nymphs repeat this process; however, after dislodging from this second host they molt into adults. Sizes of ticks in each stage can vary due to genetic and environmental conditions (Koch 1986). In laboratory settings, the life cycle can be shortened to less than 22 weeks under optimal conditions, but is usually 2 years in nature (Troughton and Levin 2007).

Seasonal peaks in the population have been reported for lone star ticks in Georgia; adult numbers peak April to June, nymphs had a bimodal distribution during May to July and August to September, whereas numbers of larvae peak July to September (Semtner and Hair 1973). Seasonality in Missouri was similar, wherein peak activity of adults was between May and July, nymphs in May to August, and larvae in July through September (Kollars et al. 2000). Anecdotal reports in Florida suggest that one of the three active stages of lone star ticks can be active in nearly every month of the year; however, peaks in activity likely are similar to those observed in Georgia.



Figure 3. Life stages of lone star ticks, *Amblyomma americanum* (Linnaeus), from top left clockwise: larva, nymph, adult male, adult female. Photograph by [Chris Holderman](#).

Eggs: Eggs (Fig. 4) are glossy, brown, oval structures that are approximately 0.4 mm in width by 0.5 mm in length (NCIPMI 1998). Eggs are deposited by engorged females in the spring, summer, and autumn. Survival rates were highest in the spring and autumn egg clutches. Incubation time in a field study was temperature dependent, ranging from 31 to 60 or more days. However, desiccation of the eggs readily occurred when soil moisture was low (< 3%) and soil surface temperature was greater than 40°C or 104°F (Patrick and Hair 1979). Because a female lays all of her eggs at one time, they are typically found in a large mass.



Figure 4. Female lone star tick, *Amblyomma americanum* (Linnaeus), with egg mass. Photograph by [Lyle Buss](#).

Larvae: Larvae, typically called “seed ticks” due to their small size and abundance (Fig. 5), are 0.5 to 1.0 mm long and have six legs (NCIPMI 1998). If humidity and temperature are favorable the larvae can survive for up to six months in the environment, but typically the larval stage is shorter due to acquisition of a suitable host (Troughton and Levin 2007). After feeding on the host for 4 to 9 days, the larva drops off and, in 3 to 4 weeks, molts into the nymphal stage (Troughton and Levin 2007). When larvae are encountered before host location, several thousand of them can be in a small area.



Figure 5. Lone star tick, *Amblyomma americanum* (Linnaeus), larva dorsal view. Photograph by [Chris Holderman](#).

Nymphs: Nymphs (Fig. 6) are 1.5 to 2.5 mm in length and have eight legs (NCIPMI 1998). Nymphs can survive for up to six months without feeding on a host. Once a host is located they feed for 3 to 8 days, drop off the host and molt into the adult stage within a 5 to 6 week period (Troughton and Levin 2007).



Figure 6. Lone star tick, *Amblyomma americanum* (Linnaeus), nymph. Photograph by [Chris Holderman](#).

Adults: Adults (Figs. 7 and 8) are 3 to 4 mm in length and have eight legs. Adults can survive 8 months to 2 years without feeding if temperature and humidity are favorable (Troughton and Levin 2007). Mating occurs on the host. The male must feed to produce spermatophores, and the female must feed to produce eggs (Troughton and Levin 2007). Blood meals increase female size drastically (Figs. 4 and 9). While feeding the female emits pheromones that stimulate the male to detach, locate the female, and mate with her (Sonenshine 2004). Males may mate with multiple females before dying. Once the female mates, she blood-feeds for several days, reaching an engorged state and then leaves the host to find a location to lay her eggs. After laying her eggs, the female dies (NCIPMI 1998).



Figure 7. Non-blood fed adult female lone star tick, *Amblyomma americanum* (Linnaeus). Photograph by [Lyle Buss](#).



Figure 8. Adult male lone star tick, *Amblyomma americanum* (Linnaeus). Photograph by [Lyle Buss](#).



Figure 9. Blood-fed, engorged female lone star tick, *Amblyomma americanum* (Linnaeus). Photograph by [Lyle Buss](#).

Hosts [\(Back to Top\)](#)

Although ticks are mobile, hosts are the primary means of tick dispersal for all active life stages (Barnard et al. 1988). The lone star tick is very aggressive and non-specific when seeking hosts (Goddard and Varela-Stokes 2009), although some specificity does occur within each life stage. The lone star tick can be found on humans, domesticated animals (e.g. cattle, dogs, horses, goats), ground-dwelling birds (e.g., quail and wild turkeys), and small (e.g. squirrels, opossums, hares) and large (primarily white-tailed deer and coyotes) wild mammals (Cooley and Kohls 1944, Bishopp and Trembley 1945, Kollars et al. 2000). Larvae primarily are collected from birds and mammals, but not on small rodents, while nymphs feed on all of these animals (Barnard et al. 1988, Kollars, et al. 2000). Adults typically feed on large- or medium-sized mammals, but can be found on small rodents and wild

turkeys. With the exception of wild turkeys, adult lone star ticks infrequently feed on birds (Barnard et al. 1988, Kollars et al. 2000, Mock et al. 2001).

Medical and Veterinary Importance [\(Back to Top\)](#)

The lone star tick is the most common tick reported to bite humans in the southeastern and southcentral U.S.A. (Masters et al. 2008). Various pathogens have been shown to enter the tick by blood feeding; however, most are not transmitted because the tick is not a competent vector (Goddard and Varela-Stokes 2009). An unknown pathogen has been implicated in causing Southern tick-associated rash illness (STARI) in humans, but etiology, pathogenicity and identification are pending (CDC 2011a). Several pathogens are known to be transmitted by the lone star tick and given the proper circumstances they may manifest into disease. These include ehrlichiosis, rickettsiosis, tularemia and protozoan infections. The causative agents of ehrlichiosis, rickettsiosis, and anaplasmosis are all tick-borne bacterial infections that are readily treatable in humans, but the causative agent can be difficult to determine because the similarities among the pathogens.

Recently, in three case studies, including one specifically identified as a result of a bite by a lone star tick, tick bites may have been involved in producing or generating an immune response that caused a food allergy to red meat proteins (Wolver et al. 2009). Heavy infestations of lone star ticks also have been associated with increased mortality in white-tailed deer fawns in Oklahoma (Bolte et al. 1970).

Southern Tick-Associated Rash Illness - STARI

STARI, also known as Masters disease, is a medical condition with a currently unknown etiology, the pathogen of which is suspected by some scientists to be transmitted by the lone star tick (CDC 2011a, Masters et al. 2008). STARI was first thought to be Lyme disease, caused by *Borrelia burgdorferi* infections, but this hypothesis has been dismissed due to the inability of the lone star tick to transmit the *Borrelia burgdorferi* spirochete, as well as the bacteria being digested within the tick (Mukolwe et al. 1992).

A spirochete was isolated from a STARI patient and named *Borrelia lonestari*; however, the next two-dozen STARI patients were not infected with *Borrelia lonestari* (CDC 2011a). The symptoms usually manifest within seven days after a lone star tick bite, with a rash expanding three inches or more from the bite location (CDC 2011a). STARI patients usually exhibit fatigue, fever, headache, and joint and muscle pain, but symptoms have been resolved following antibiotic treatments (CDC 2011a). STARI is usually diagnosed within the southern U.S.A. but has been reported in one case as far north as New York state (Feder et al. 2011). The cause of STARI is currently unknown (CDC 2011a).

Ehrlichiosis

Ehrlichiosis is a disease caused by a group of obligate intracellular pathogenic bacteria, meaning they reside within the host animal's cells. Both humans and other animals can be affected. *Ehrlichia chaffeensis* is the cause of human monocytic ehrlichiosis (HME), of which the lone star tick is the primary vector to humans (CDC 2011b). White-tailed deer are thought to be an important reservoir host for *Ehrlichia chaffeensis*, while rabbits and squirrels may play a role in maintaining the pathogen in the U.S.A. (Allan et al. 2010a). Diagnosis of *Ehrlichiosis* outside of the lone star tick's range often is attributed to a misdiagnosis of anaplasmosis, a disease caused by a different pathogen (CDC 2011b). Confirmed human ehrlichiosis cases have increased annually from 142 in 2001 to 885 in 2012 (CDC 2012b).

The lone star tick transmits *Ehrlichia ewingii*, but the prevalence of this pathogen is much lower, with only 10 human cases reported in 2010 (CDC 2012b). *Ehrlichia ewingii* is likely maintained in nature by lone star ticks feeding upon ruminants, squirrels, and hares (Allan et al. 2010a).

A species of *Ehrlichia*, not yet identified, and a potential new zoonosis (animal-human disease), produces Panola mountain *Ehrlichia* (PME). This pathogen, isolated near Atlanta, GA, shows genetic

similarity to *Cowdria ruminantium*, the causative agent of the devastating disease heartwater in ruminants such as cattle (Loftis et al. 2006).

Dogs have been shown to be susceptible to infections of both *Ehrlichia chaffeensis* and *Ehrlichia ewingii*. However, dogs also are susceptible to *Ehrlichia canis* a related microbe, which is usually transmitted by *Rhipicephalus sanguineus* (Latrielle), the brown dog tick (Beall et al. 2012).

Rickettsiosis

Rickettsiosis is a disease caused by infection of one of several bacteria in the genus *Rickettsia*. These bacteria are obligate intracellular pathogens as described with ehrlichiosis. A *Rickettsia* species, similar to *Rickettsia rickettsii*, which causes Rocky Mountain spotted fever (RMSF) in humans, has been isolated from lone star ticks in a laboratory setting by Goddard and Norment (1986). *Rickettsia rickettsii* has not been found in lone star ticks. *Rickettsia parkeri* has been confirmed in laboratory transmission studies to be vectored by lone star ticks (Goddard 2003) and has been isolated from a small number of field-collected lone star ticks (Cohen et al. 2009).

Traditionally, *Rickettsia parkeri* was thought to be non-pathogenic (non-disease causing) in humans, but Raoult and Olson (1999) expressed the opinion that all rickettsial organisms should be viewed as potential human pathogens. Due to limitations in diagnosis of the specific microbe species, the CDC does not distinguish among individual bacterial pathogen species. For 2012, 3,776 cases were attributed to “probable” and 179 to “confirmed” cases of human infections of spotted fever "group" rickettsiosis in the U.S.A. (CDC 2013).

Tularemia:

Tularemia is a disease caused by a bacterium (*Francisella tularensis*) that affects many mammals, including humans, and is spread primarily by infected arthropods, including ticks, or by contact with infected mammals, usually rabbits and hares (Hopla 1960). Recently, tularemia incidence has ranged between 93 and 166 cases (2007-2011), but these are not segregated by infection type or route. However, most infections are associated with hunters handling infected rabbits (CDC 2012b).

***Theileria cervi*:**

Theileria cervi is a tick-transmitted protozoan parasite that infects white-tailed deer and attacks red blood cells. This pathogen has been linked with deer death when tick numbers and parasite numbers are substantial (Samuel and Trainer 1970). The role of *Theileria cervi* in deer mortality is somewhat unclear, however, given that some researchers have reported fawn mortality in deer populations infested with lone star ticks without the presence of *Theileria cervi* (Hair et al. 1992). The incidence rate of *Theileria cervi* increased in white-tailed deer populations from June to September, which corresponded to lone star tick activity in the area surveyed (Waldrup et al. 1992).

Management ([Back to Top](#))

Many management practices have been evaluated for the reduction of tick numbers in a local area. Typical practices are acaricide (insecticides for ticks) applications, vegetative management (controlled burning or mechanical removal of under-story brush and other plants), and host exclusion. Many involve greatly altering the biotic and abiotic factors that contribute to tick population increases.

Controlled burning over a four-year study in a wooded recreational area resulted in a significant reduction in lone star tick populations (Davidson et al. 1994). Because the tick lifecycle is 2 to 3 years in nature, tick reduction following such a management protocol may not be apparent for some time.

Treatment of deer with a "4-poster" feeder station has reduced tick numbers over time (Solberg et al. 2003). The '4-poster' feeder station attracts deer with corn. While eating the corn their ears, head and neck come in contact with acaricide-treated paint rollers. Over a three-year study, ticks (in this case, *Ixodes scapularis*) were reduced on deer (adult tick hosts) and mice (larval and nymphal tick hosts) (Solberg et al. 2003). Because lone star ticks also use deer as hosts, such an approach may work where

these ticks are found. A Tennessee study evaluated this feeder station system; however, although tick populations were reduced, the costs of such a station were high (est. \$20 per device per week) and the impact was limited in range (one station per 20 hectares, ~50 acres) (Harmon 2010).

In a study examining individual actions and combinations of acaricide application, vegetative management, and host exclusion (white-tailed deer), an integrated pest management system using all three approaches was reported to be the most effective. However, this approach was dependent on resources available (equipment, supplies and personnel costs) to implement the management practices (Bloemer et al. 1990). Altering host (white-tailed deer) behavior by removing an invasive shrub was shown to alter deer habitat preference and therefore tick prevalence in the habitat (Allan et al. 2010b).

The use of a repellent or pesticide, correctly applied to clothing and on gear following specific product label instructions, is considered the best tick bite prevention as recommended by the CDC (2012a). Wearing light colored clothing, inspecting clothing, gear, and pets, conducting a full body tick check, and showering after being outdoors are all recommended steps toward preventing tick bites. For protection of cats and dogs against tick bites, please refer to the EDIS publications below and consult with your veterinarian.

For more information see the [UF/IFAS Insect Management Guide for ticks](#).

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Red meat allergies likely result of lone star tick

by Craig Boerner (<http://news.vanderbilt.edu/author/boerner-craig/>) | Thursday, Feb. 20, 2014, 2:00 AM

Tennessee, North Carolina and Virginia Seeing Numerous Cases



(<http://news.vanderbilt.edu/2014/02/red-meat-allergies-likely-result-of-lone-star-tick/lonestartick-2/>)

The lone star tick is widespread in the United States and is most common in wooded areas. (CDC Public Image Library)

Lone star tick bites are likely the cause of thousands of cases of severe red meat allergies that are plaguing patients in Southeastern states including Tennessee, North Carolina and Virginia and spreading up the Eastern Seaboard along with the deer population.

Vanderbilt's Asthma, Sinus and Allergy Program (A.S.A.P.) clinic (<http://www.vanderbilthealth.com/asap/>) is seeing one or more new cases each week of patients allergic to the alpha-gal sugar present in red meat, according to [Robert Valet](http://www.vanderbilthealth.com/main/findadoc?doc=1780731661) (<http://www.vanderbilthealth.com/main/findadoc?doc=1780731661>), M.D., assistant professor of Medicine.

"It is not completely understood exactly how the allergy starts," Valet said. "The thought is that the tick has the alpha-gal sugar in its gut and introduces it as part of the allergic bite and that causes the production of the allergy antibody that then cross-reacts to the meat," he said.



<http://news.vanderbilt.edu/2014/02/red-meat-allergies-likely-result-of-lone-star-tick/robert-valet-allergy-pulmonary-and-critical-carephotos-by-susan-army/>

Robert Valet, M.D

Valet said the allergy can cause hives and swelling, as well as broader symptoms of anaphylaxis including vomiting, diarrhea, trouble breathing, and a drop in blood pressure.

"I think it is something that certainly belongs among the most important food allergies, particularly in the Southeast," he said. "Certainly these patients can present with every bit as severe of an allergy as someone who is allergic to peanuts."

Alpha-gal patients can safely eat poultry such as chicken or turkey but red meats such as beef and pork, and even game like venison, will cause a reaction. Valet said some patients react to milk, even in relatively small amounts.

Persons with the allergy can go into a delayed anaphylactic shock four-six hours after eating red meat, so when Hendersonville resident September Norman woke up in the middle of the night with a swollen tongue and hives she wasn't sure the source of her problem.

Norman and her husband were staying at Tennessee's Fall Creek Falls State Park at the end of July, had played some golf and grilled rib eye steaks for dinner.

"At about midnight I woke up and was itching very bad, kind of like a rash," she said. "About 2:30 a.m. I got up and my hands felt like they were on fire, like I was bitten by fire ants. I drank two bottles of water, sat on the sofa, and it wasn't five minutes before I felt my tongue and lip swelling and told my husband that something was wrong. I could barely talk at that point my tongue was so thick. He turned on the lights and his eyes looked like saucers."

They drove from the park toward the interstate to get a cell phone signal to call 911 and waited on the highway for emergency help to arrive.

"I was getting worse. My whole body was red and broken out in hives. I was staring out the window, saying 'Please God, not here.' I probably would have gone into a panic had I looked at myself in the mirror. My husband said my face looked like a giant red balloon and my lips looked like a clown."

The emergency responders gave Norman an epinephrine injection to treat the anaphylaxis and she received Benadryl, an IV, and steroids during the ambulance ride to Sparta, the closest hospital. The doctor at the hospital said her reaction was probably environmental and sent her home with a prescription and advice to always carry an EpiPen.

She continued to eat red meat, even preparing her son's favorite pork tenderloin dish that Wednesday. As the week wore on, and her steroids from the hospital wore off, Norman felt her throat becoming tighter and tighter.

"I had been eating the culprits all week," she said. "I was full of steroids and that's probably why it took so long. We went to Vanderbilt and Dr. Jan Price (<http://www.vanderbilthealth.com/primarycare/findadoc?doc=1790884138>) talked to me about what happened to me. I was retracing my steps and remembered that, in the middle of June, a tick bit me on the foot. She sent me to Dr. Valet and he said he knew what I had based on the tick and my reactions."

Valet said he diagnoses patients with a blood test but there is not a good way to desensitize people once they become allergic to this food, so they have to avoid red meats and, in some cases, milk as well.

"It certainly is a big disruption for a lot of people's lives. Things like your classic barbecue really becomes off limits," Valet said. "We know that getting repeated tick bites causes the level of allergy antibody to rise and so we do recommend people with this allergy do good tick avoidance and carry an EpiPen if they do have an exposure to red meat and need to rescue themselves."

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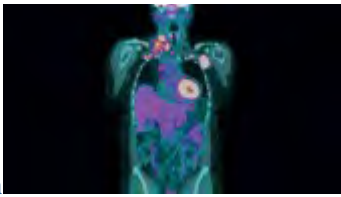
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Delayed Anaphylaxis to Red Meat in Patients with IgE Specific for Galactose alpha-1,3-Galactose (alpha-gal)

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Abstract

Anaphylaxis is a severe allergic reaction that can be rapidly progressing and fatal. In instances where the triggering allergen is not known, establishing the etiology of anaphylaxis is pivotal to long-term risk management. Our recent work has identified a novel IgE antibody (Ab) response to a mammalian oligosaccharide epitope, galactose-alpha-1,3-galactose (alpha-gal), that has been associated with two distinct forms of anaphylaxis: (1) immediate onset anaphylaxis during first exposure to intravenous cetuximab, and (2) delayed onset anaphylaxis 3–6 h after ingestion of mammalian food products (e.g., beef and pork). The results of our studies strongly suggest that tick bites are a cause, if not the only significant cause, of IgE Ab responses to alpha-gal in the southern, eastern and central United States. Patients with IgE Ab to alpha-gal continue to emerge and, increasingly, these cases involve children. This IgE Ab response cross-reacts with cat and dog but does not appear to pose a risk for asthma; however, it may impair diagnostic testing in some situations.

Keywords

Anaphylaxis; Delayedanaphylaxis; Alpha-gal; Galactose; Food allergy; IgE; Mammalian meat; Tick bites; Asthma; Red meat

Introduction

When the syndrome of delayed anaphylaxis to red meat was first described in 2009, the report included details on 24 cases [1]. Within a year, it was obvious that the cases should be counted in hundreds rather than dozens. By 2012, it was clear that there are thousands of cases across a large area of the southern and eastern US [2•]. Furthermore, it is clear that the same syndrome is present in several countries in Europe and also in Australia [3–6]. The syndrome came to light because of an enigmatic regional prevalence of anaphylactic

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Dr. Platts-Mills has served as a consultant for IBT Laboratories.

reactions to the monoclonal antibody cetuximab [7]. It was investigation of those cases which established that they were causally related to pre-existing IgE antibodies to an oligosaccharide on the FAB portion of the monoclonal Ab [8]. That oligosaccharide, galactose alpha-1,3-galactose (alpha-gal), is a major blood group substance of the non-primate mammals, and is well recognized as a target of IgG antibodies which are present in the serum of all immunocompetent individuals [9]. Since that time, it has become clear that these IgE antibodies are strongly associated with the syndrome of delayed anaphylaxis to red meat [1], and also that the predominant, if not exclusive, cause of these IgE antibodies in the USA is bites from the lone star tick *Amblyomma americanum* [10••].

Section I

Geographic Distribution of IgE Antibodies to Alpha-gal and Delayed Anaphylaxis

a) Within the United States—The distribution of these antibodies first became clear from the states in which reactions to cetuximab were occurring, i.e. Virginia, North Carolina, Tennessee, Arkansas, Oklahoma, and Missouri [8]. Subsequently, it has become clear that the syndrome of delayed anaphylaxis to red meat is most common in these same states [1]. In fact, it was the similarity between the region for reactions to cetuximab and the maximum incidence of rocky mountain spotted fever that suggested that tick bites might be relevant to these reactions [10••]. Subsequently, evidence came from many different sources supporting the idea that tick bites were the primary cause of those antibodies in the United States [2•, 10••, 11]. Evidence that the lone star tick is the primary cause has come from individual cases, from the correlation between IgE antibodies to alpha-gal, and IgE antibodies to this tick, and from the known distribution of the tick [10••]. This tick is being followed closely by the Centers for Disease Control and Prevention (CDC) because it is the primary vector of Ehrlichiosis [12–14]. Interestingly, there is good evidence both from the CDC and also from the army that the lone star tick is steadily expanding its range [15•].

While it is easy to argue that, with the increasing number of deer, ticks and tick bites have caused a progressive increase in the disease, that would be more difficult to prove. We have case histories and serological evidence that the IgE antibodies and the syndrome existed in the 1980s. On the other hand, it would be difficult to estimate the prevalence of a syndrome 30 years before it had been described. It is important to remember that there are two distinct elements: the production of IgE antibodies and the urticarial or anaphylactic reactions to red meat.

b) Prevalence and distribution of delayed anaphylaxis outside the USA—The first report that tick bites could give rise to allergic reactions to meat was made by Dr. Sheryl Nunen to the Sydney Allergy Society in 2006. She published those results in 2009, and subsequently Mullins et al. confirmed in 2012 that patients in Australia with reactions to mammalian meat have IgE Ab to alpha-gal [3, 4]. By contrast, there were already reports from Europe of similar cases [5, 6]. In particular, the food allergy group in Nancy in France reported cases in 2009, and have recently reported evidence that kidneys are particularly rich in alpha-gal [16••]. Reports of delayed anaphylaxis have also come from Dr. Van Hage and her colleagues in Stockholm and from Dr. Uta Jappe in Germany [6, 17]. In each case, they have confirmed that the patients had serum IgE antibodies specific for galactose-alpha-1,3-galactose. Although cetuximab is not as widely used in Europe as in the United States, there have been reports of immediate reactions including a recent death from France [18]. The tick species that appears to be responsible for these responses in France is *Ixodes ricinus*, while in Australia it is *Ixodes holocyclus* [3, 4, 16••].

c) IgE antibodies to alpha-gal in countries where helminth and ecto-parasites are common—Oligosaccharides are well recognized as a target for antibody response to

helminths [19, 20]. In addition, it is well recognized that helminth and ecto-parasites such as scabies can give rise to IgE antibody responses. Two reports from Africa have shown the presence of IgE antibodies to alpha-gal in sera from children and adults [21, 22]. Dr. Sibanda in Zimbabwe working with Drs. Van Hage and Valenta have reported that IgE antibodies to alpha-gal are common in Harare, but they did not discuss reactions to meat [23 ••]. Similarly, we have reported a high prevalence of IgE antibodies to alpha-gal among children in a rural village 100 miles north of Nairobi [10 ••]. Interestingly, in both cases, the antibodies were initially thought to be specific for cat [21, 23••]. In the Kenyan village, we were not aware of reactions to meat, but the children were not directly questioned [21]. At present, it would be difficult to identify the stimulus that gives rise to IgE antibodies to alpha-gal in sub-Saharan Africa—possible candidates include cestodes, nematodes, scabies, ticks, and a variety of other ecto-parasites. What is potentially very interesting is that there are no reports of delayed anaphylactic or urticarial reactions to red meat in sub-Saharan Africa. If this is true, it could provide an important insight into the mechanism of the delayed reactions.

Section II

IgE Antibodies to Alpha-gal are not Associated with Rhinitis or Asthma

In the early studies on patients, who presented with delayed anaphylaxis to red meat, two things were obvious: (1) these patients gave positive skin tests and blood tests for cat, and (2) they did not report allergic symptoms related to cat exposure [1]. From several types of study, it became clear that the sensitivity to cat extracts could be explained by IgE antibodies binding to alpha-gal on cat-derived proteins. The best defined of these proteins is cat IgA. In 2007, Gronlund and his colleagues in Sweden recognized the presence of an oligosaccharide epitope on cat IgA [24]. After the recognition of IgE Ab to alpha-gal, it was established that the epitope on cat IgA was alpha-gal [17]. In addition, it is well established that all mammalian thyroglobulins are heavily “decorated” with alpha-gal [25]. By contrast, many proteins which are important targets for IgE antibody responses, such as Fel d 1 and cat albumin, are not glycosylated with alpha-gal [17]. Recently, we have investigated a large group of patients, who presented with delayed symptoms after eating red meat, for history of symptoms, lung function, and evidence of lung inflammation. The results provide compelling evidence that IgE Ab to alpha-gal do not create a risk for asthma [2•]. Initially, we found that in vitro assays for IgE Ab to cat extract were consistently positive in patients with IgE to alpha-gal [1]. However, this is much clearer using epithelial extracts which include multiple proteins present in the pelt than with extracts made from “dander” only (Fig. 1). Recently, the immunoCAP assay for IgE to cat was changed to become purely dander, and as a result it is in effect an assay for Fel d 1, and may underestimate IgE to cat albumin or alpha-gal [2•].

The results on asthma included a study on acute asthma in the University of Virginia emergency department, where we had previously found confusing data, with a higher than expected prevalence of IgE to cat among controls [26, 27]. Further analysis of those sera showed that the IgE antibodies to cat included IgE to both alpha-gal and Fel d 1. The IgE to alpha-gal showed no association with asthma while IgE Ab to Fel d 1 was highly significantly associated with asthma [2•]. The results together provide strong evidence that the risk of asthma is related to protein allergens which are inhaled (Fig. 1). Equally, the evidence argues that IgE antibodies to alpha-gal provide an excellent model of the kind of IgE responses that can be induced by parasites but are not related to rhinitis or asthma.

Interestingly, the studies on the relevance of ticks and those on the risk of asthma provided some insight into the prevalence of these IgE antibodies in the community. The apparent prevalence in Virginia, Tennessee, and North Carolina may be as high as 10 % [10••]. This

raises a question to which we only have tentative answers, that is what proportion of subjects with IgE Ab to alpha-gal experience urticaria or anaphylactic reactions to red meat. Our best estimate from the number of cases in central Virginia is that the true value is unlikely to be greater than 10 %.

Section III

Description of Pork–Cat Syndrome

Despite meat being an important source of protein in western diets, development of meat allergy is uncommon [28]. This paradox may not be unexpected for mammalian meat, however, as the extensive homology of plasma and tissue proteins across mammalian species decreases the likelihood of a specific IgE response [29, 30]. In fact, when clinically relevant reactivity to meats has been demonstrated, the results point to cross-reactivity among the identified proteins (e.g., bovine serum albumin, serum gamma globulins, actin, and tropomyosins) and not to a sensitization with meat-specific epitopes [31]. The syndrome of delayed anaphylaxis due to IgE Ab to alpha-gal is different in that the IgE antibodies bind to a specific oligosaccharide which is present on proteins and lipids from a large number of non-primate mammals. Among the cross-reactive syndromes, however, is the notable “pork–cat syndrome” [32, 33]. In this uncommon syndrome, patients develop an IgE Ab response specific for cat serum albumin that cross-reacts with porcine albumin and can lead to severe or even fatal allergic reactions when pork is consumed [32–34]. Interestingly, the reported cases of pork–cat syndrome are largely European. In our ongoing evaluation of delayed anaphylaxis or urticaria after the consumption of mammalian meat due to IgE Ab to alpha-gal [1], we have evaluated sera from numerous patients with suspected “meat allergy”. Mainly because of this focus, we have identified several cases of pork–cat syndrome in the US.

Published data regarding pork–cat syndrome have suggested that sensitization to cat albumin represents the primary event in the development of the cross-reactive IgE [33]. In most instances, patients with pork–cat syndrome have cat exposure (often ownership in our experience); positive responses on skin test to cat dander or pork; and report inconsistent (but not delayed) reactions after eating pork. The fact that reactions are not delayed has been an important clue in our evaluation of patients as this aspect is *not* in keeping with symptoms following red meat exposure in patients with IgE Ab to alpha-gal [1]. Moreover, in general patients with pork–cat syndrome, neither react to beef nor have serum evidence of sensitization [32, 33]. Again, this creates a distinction from patients with IgE Ab to alpha-gal, where serum IgE to beef is uniformly present [1].

Pork–cat syndrome is similar to other food allergies in that a range of presentations are seen (from oral itching to anaphylaxis), and the clinical symptoms are not consistently predicted by the titer of IgE to the allergen, cat serum albumin. Similar to delayed anaphylaxis from IgE Ab to alpha-gal, pork–cat syndrome can affect children and adults. Although pork–cat syndrome does not appear to be related to tick bites, both syndromes do not arise early in life: most reported patients are older than age 5 with the majority being adults or teens [32–34]. It appears that the primary sensitization to cat serum albumin develops over time and, therefore, the onset of a “new” food allergy in an older child or adult may merit consideration of pork–cat syndrome as a diagnosis, especially if a history of tick bites is absent.

Interestingly, and not unusual for meat allergy, patients do not report reactions with each instance of eating pork. Hilger et al. also address this point and, further, state that only one-third of appropriately sensitized patients report allergic symptoms in relation to pork consumption [33]. This has been in keeping with our experience and may be due to high

cooking temperatures which can cause the albumin to denature [33]. In patients with pork–cat syndrome, reactions to pork begin soon after eating the meat. Both pork–cat and alpha-gal food allergies are IgE-mediated, involve mammalian meat, and can show similar responses with certain skin tests and immunoassays; however, symptoms from pork–cat syndrome usually occur within 30–45 min and can occur as rapidly as oral itching during the meal. Due to the inconsistency of these reactions (likely owing to the preparation of the meat), there may not be a simple or obvious pattern to suggest that pork is the culprit food. Hence, if a careful history reveals the possibility that mammalian meat could be associated with episodes, we suggest performing immunoassay testing for sIgE to pork, beef, cat serum albumin, and alpha-gal. Further investigations may be required, but this simple panel would identify patients whose symptoms were most likely to be explained by pork–cat syndrome.

Section IV

IgE Ab to Alpha-gal in Children

One of the interesting aspects recently of delayed meat allergy has been the emergence of numerous cases in children. While we had diagnosed children with IgE Ab to alpha-gal in central Virginia, we have now been made aware of children presenting with IgE Ab to alpha-gal in numerous centers throughout the eastern and central United States. Colleagues at Duke University (Dr. Michael Land and Dr. Moira Breslin), Kansas City Children’s (Dr. Paul Dowling and Dr. Tara Federly) and in East Hampton, New York (Dr. Erin McGintee) have diagnosed pediatric patients with IgE Ab to alpha-gal and the characteristic delayed reactions to mammalian meat. In most instances, these children were seen by allergists; however, a few of the cases were diagnosed in emergency departments. Unlike their adult counterparts who frequently present with anaphylaxis, it has been our experience that the majority of children with this syndrome present with urticaria rather than acute episodes of delayed anaphylaxis. In keeping with published data regarding tick bites giving rise to the IgE Ab to alpha-gal in adults [15•], children with alpha-gal allergy also report a history of tick bites (unpublished data).

Children who develop IgE Ab to alpha-gal may have positive skin, intradermal or immunoassay, testing to milk, beef, pork, cat, or dog [11]. It is important to understand that many children suffer from milk allergy, but IgE to alpha-gal is distinct from the more traditional, protein-based cow’s milk allergy. Alpha-gal-related reactions are present in older children, many of whom have no history of either food allergy or any allergic disease [1]. Clinicians should recognize that the carbohydrate moiety galactose-alpha-1,3-galactose is found in mammalian milk as evidenced by the positive immunoassay results to cow’s milk and goat’s milk. Therefore, in a patient who has an apparent new onset milk allergy over the age of 5, IgE Ab to alpha-gal should be considered as an alternative diagnosis to protein-based milk allergy. In our experience, we have not a priori removed milk or dairy products from the diet of adults with this syndrome if they have previously tolerated these products. We have continued a similar approach in the pediatric population, unless the allergic episodes persist, at which time we would suggest removing dairy products from the diet.

While there are multiple potential causes for both acute and chronic urticaria, as well as angioedema and idiopathic anaphylaxis, physicians should keep the syndrome of delayed reactions to mammalian meat in mind in pediatric patients. IgE Ab to alpha-gal should be diagnostically considered in children with chronic urticaria, angioedema, or idiopathic anaphylaxis, particularly in those patients living in areas where the lone star tick is common or where the history is consistent with the disease syndrome, including delayed symptoms after ingestion of beef, pork, lamb, or even milk.

Section V

Delayed Reactions: Clinical Experience and Impressions

Since establishing the assay for IgE Ab to alpha-gal, large numbers of sera have been screened. The results showed that these IgE Ab were regionally distributed and that they were also associated with a novel form of anaphylaxis. As mentioned, these patients reported delayed symptoms after eating mammalian meat but they had had no trouble with chicken, turkey, or fish [1, 11, 35]. Thus, their symptoms matched the specificity of IgE antibodies present in their serum, which accurately reflected the known distribution of alpha-gal in mammals [1, 36]. The nuances of the delayed reactions seem to reflect that dose, temporal proximity to tick bites and composition of meat are important in influencing the allergic reactions. Food challenge studies with research subjects have shown that a relatively small amount of mammalian meat (i.e. a single strip of bacon) is frequently tolerated without clinical evidence of a reaction. Large doses are not required, however, as two pork sausage patties (~86 g) reliably induces clinical symptoms in our challenge studies. When patients and subjects do consume larger doses of mammalian meat, such as a double hamburger, rack of ribs, or a plate of barbecue, the reactions are often more severe in nature with several organ systems affected (i.e. anaphylaxis).

Similarly, food challenge studies and several hundred case descriptions have taught us that fattier meats (or mammalian products such as pork rinds) provoke episodes more consistently and the reactions are more severe. In fact, many patients describe having eaten lean meats such as deli ham or venison tenderloin without any evidence of a reaction, whereas having spare ribs the same week has led to emergency treatment. Another facet of the mammalian meat syndrome is that reactions to red meat, and even dairy, can be easier to elicit in the setting of recent tick bite(s) (1–4 weeks). The IgE Ab to alpha-gal appears to decrease over time, but this trend can be reversed by additional tick bites [10••]. Thus, patients can be led to believe that they are no longer allergic to mammalian meat because they have eaten small amounts of meat without reactions (likely, their IgE Ab to alpha-gal has fallen quite low). Overall, the factors which feed into the equation to produce a reaction are clearly complex and variable, especially in the setting of an IgE Ab to alpha-gal that may ‘naturally’ decrease over time. It is not surprising that many of these cases have only been diagnosed over the course of years.

The reason(s) for the 3–6-h delay in this IgE-mediated food allergy has not yet been elucidated. Given the apparent role for lipids in producing the clinical reaction, it may well be that absorption of lipid is the rate-limiting step in the delay. Biochemically, fats are absorbed and processed much differently than are carbohydrates and proteins. Fats ultimately enter the bloodstream via the thoracic duct 3–4 h after a meal. The conversion and processing of fats to chylomicrons and then further in LDL particles of various sizes may also explain a portion of the delay. Alternatively, chylomicrons themselves may transport alpha-gal antigens from the gut and intestinal epithelium via mesenteric lymph nodes to the circulation [37]. Intestinal epithelial cells have been postulated to secrete antigen on newly formed chylomicrons [37], a process that could also help to explain the delayed response to mammalian meat in patients with IgE Ab to alpha-gal.

Conclusions

The discovery of IgE Ab to the oligosaccharide galactose alpha-1,3-galactose has made it possible to investigate several novel aspects of allergic disease. These IgE Ab bind to a wide range of mammalian proteins, and we recognized the syndrome of “delayed anaphylaxis to mammalian meat” [1, 11]. However, the most interesting feature of the reactions may be that first symptoms 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. Moreover, understanding how ticks induce this form of response will be important as we explore the control of IgE Ab responses in general.

Acknowledgments

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Abbreviations

alpha-gal	galactose- α -1,3-galactose
Ab	antibody

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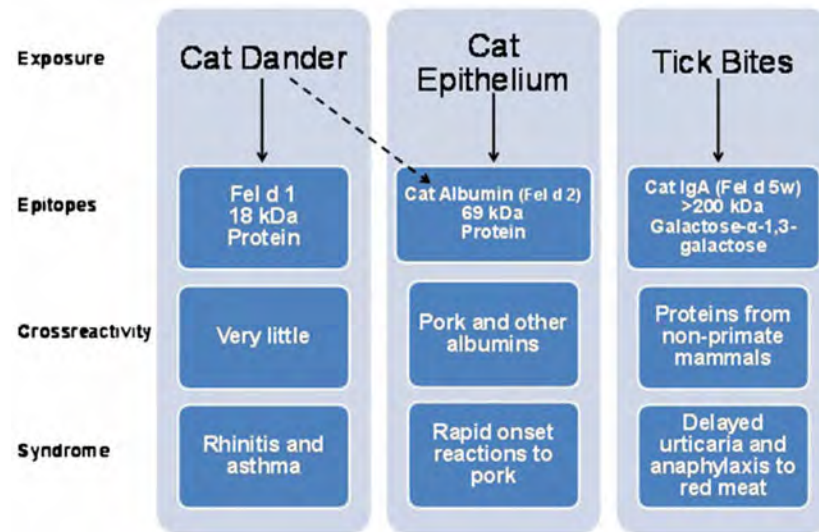


Fig. 1. Comparison of cat exposure (direct or indirect) and the IgE response to cat-related proteins in terms of epitope, cross-reactivity, and the allergic syndrome

Arkansas Poison Control

24/7/365

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UAMS College of Pharmacy

Arkansas Poison Control Center

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Arkansas Poison Control Center








 Confidential helpline

 24 hr/day, 365 days/year

 Health care professionals

 General public

 Free resource

-  Treatment advice
-  Follow-up
-  Emergency drug information
-  Non-emergent drug information based on triage
-  Prevention measures
-  Professional & public education
-  Statistical data

If you call the AR Poison/Drug Information Center who will you talk to?

- ☠ Nurses (6) & Pharmacists (6)
 - ☠ Certified poison specialists (CSPI)
 - ☠ 2-DABAT
- ☠ Medical director
 - ☠ (MD, Ph.D., ABMT)
- ☠ Support staff (Supervised Pharmacy or Medical students)



Alpha Gal Thoughts/Concerns

- Gluten is probably the most similar type call.
- Medication Lists
 - Manufacturers
 - Lot #'s
 - Expiration Dates
 - Ingredient lists



Thoughts/Concerns Cont.

- Unless the manufacturers are testing; they will default to “We can’t guarantee.....”
- Searches will take time.





"Bummer of a birthmark, Hal."



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The relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose

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Abstract

Background—We have observed patients clinically allergic to red meat and meat-derived gelatin.

Objective—We describe a prospective evaluation of the clinical significance of gelatin sensitization, the predictive value of a positive test and an examination of the relationship between allergic reactions to red meat and sensitization to gelatin and alpha-Gal.

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Conflict of interest statement

Dr Mullins has received unrestricted investigator-initiated grants from Commonwealth Serum Laboratories Australia and Alphapharm Australia (the past and current Australian distributors of EpiPen), Abbott Nutrition Australia and the Ilhan Food Allergy Foundation within the last 5 years. Dr Commins is a volunteer committee member for the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology and is an author for Up-to-Date. Dr. Platts-Mills has a patent on the use of streptavidin solid phase to evaluate IgE antibodies to recombinant molecules.

Methods—Adult patients evaluated 1997-2011 for suspected allergy/anaphylaxis to medication, insect venom or food were skin tested with gelatin colloid. In vitro (ImmunoCap) testing was undertaken where possible.

Results—Positive gelatin tests were observed in 40/1335 individuals; 30/40 patients with red meat allergy (12 also clinically allergic to gelatin); 2/2 with gelatin colloid anaphylaxis; 4/172 with idiopathic anaphylaxis (all responded to intravenous gelatin challenge of 0.02 to 0.4g); 4/368 with drug allergy. Testing was negative in all patients with venom allergy (n=241), non-meat food allergy (n=222), and miscellaneous disorders (n=290). ImmunoCap was positive to alpha-Gal in 20/24 meat allergics and in 20/22 with positive gelatin skin tests. The results of gelatin skin testing and anti-alpha-Gal IgE were strongly correlated ($r=0.46$; $P<0.01$). Alpha-Gal was detected in bovine gelatin colloids at concentrations of ~ 0.44 to 0.52ug/gm gelatin by inhibition radioimmunoassay.

Conclusion—Most patients allergic to red meat were sensitized to gelatin and a subset was clinically allergic to both. The detection of alpha-Gal in gelatin and correlation between the results of alpha-Gal and gelatin testing raises the possibility that alpha-Gal IgE may be the target of reactivity to gelatin. The pathogenic relationship between tick bites and sensitization to red meat, alpha-Gal and gelatin (with or without clinical reactivity) remains uncertain.

Keywords

food allergy; anaphylaxis; red meat; alpha-galactose; gelatin; colloid

INTRODUCTION

Allergic reactions to red meat are relatively uncommon, responsible for 3% of food allergy (FA) cases in some series, as recently reviewed (1). Beef is the most commonly reported meat allergen, with up to 20 percent of cow's milk-allergic children reported as being beef allergic (2). Previous studies describe bovine serum albumin and bovine IgG as the dominant beef allergens, and to a lesser extent, muscle-derived proteins such as actin, myosin or tropomyosin (3). Allergic reactions to bovine and porcine-derived gelatin are less commonly described (4-8), but clinical reactivity to red meat and gelatin in the same patient has not previously been reported. Nonetheless, gelatin is an ingredient of some processed foods (9), gelatin colloids (10) and as stabilizing agents in some vaccines (11, 12), and is thus potentially a cryptic allergen. Finally, adverse reactions to pork, lamb, rabbit, chicken and turkey are relatively uncommon with case reports of kangaroo, seal and whale meat allergy reflecting different regional exposures (13-18).

Recent research has demonstrated the importance of the IgE response to the cross-reactive carbohydrate determinant galactose-alpha-1,3-galactose (alpha-Gal) as a potential mediator of adult onset red meat allergy (19), and a possible relationship with exposure to tick bites in Australian (20) and USA (21) studies. The fortuitous observation of one patient allergic to red meat and topical gelatin (4) and two patients with initial anaphylaxis to intraoperative gelatin colloid followed by anaphylaxis to red meat on separate occasions (5) prompted a prospective 14-year evaluation of the clinical significance of gelatin sensitization, the predictive value of a positive skin test and an examination of the relationship between allergic reactions to red meat and sensitization to gelatin and alpha-Gal.

PATIENTS AND METHODS

Study Population

The study was undertaken in a mixed adult/pediatric specialty allergy/immunology practice in the Australian Capital Territory in South-Eastern Australia. The practice services the local inland metropolitan population and surrounding regional (including coastal) areas. Referrals were received from general medical practitioners, accident and emergency departments and pediatricians. Patients were assessed by the first author (RJM). Clinical and demographic data were entered prospectively into a searchable database (Blue Chip Clinical Research Module, Health Communication Network, Sydney; Microsoft Access, Microsoft Corporation, Redmond, WA, USA). Data (and accuracy) were analyzed and verified retrospectively. The characteristics of all patients aged ≥ 18 years evaluated in the calendar years 1995 to 2011 were analysed. The Human Research and Ethics committee (Calvary Bruce/Calvary John James Private Hospitals) approved the study.

Patient evaluation

Glycerinated commercial food allergen extracts (beef and pork; Hollister Stier, Spokane, WA, U.S.A) and histamine 10 mg/ml positive control (Hollister Stier) were purchased from Link Pharmaceuticals Australia (Sydney). In the absence of commercial extracts (in Australia) for lamb, kangaroo or horse meat allergy testing, a fresh 10% weight/volume slurry was prepared using ground meat in saline, with the supernatant used for skin prick testing (SPT) when required. Bovine gelatin-derived colloids Haemacel (35 mg/ml gelatin) and Gelofusine (40 mg/ml gelatin) were purchased from Aventis Pharma (Sydney, Australia) and B. Braun (Castle Hill, NSW, Australia), respectively. Gelatin in these products is extracted from bovine bones only, excluding the skull (Hartley Atkinson, AFT Pharmaceuticals; Howard Johnson, B Braun Pharmaceuticals, personal communications, 2007), using a combination of acid and alkaline hydrolysis, followed by heat extraction at temperatures up to 90°C, then sterilised at temperatures $>100^\circ\text{C}$. SPT testing and intradermal testing (IDT) were performed on the volar aspect of the forearm and interpreted according to standard guidelines (22). SPT was performed using metal lancets (Stallergenes, Antony, France). A positive SPT was defined as a wheal size of at least 3 mm greater than a negative control (saline) at 15 minutes. Insulin syringes with 27 gauge needles were used for IDT to introduce $\sim 0.02\text{ml}$ allergen. A positive IDT was defined as a wheal ≥ 5 mm greater than the negative control (saline) at 15 minutes, accompanied by itching and surrounding flare. SPT and IDT results were recorded as the mean wheal diameter. Undiluted Haemacel and Gelofusine were used for SPT and IDT. When SPT with beef, pork were negative, IDT was undertaken with the same commercial extracts freshly diluted 1/100 in saline as previously described (19). When SPT with gelatin colloid was negative, IDT was undertaken using undiluted colloid. The primary indication for undertaking SPT/IDT was a history of possible red meat and/or gelatin allergy. Secondary indications (for research purposes) were suspected drug, insect venom allergy or FA/anaphylaxis, where most adults with anaphylaxis ($>90\%$) assessed between 1997-2011 were tested as well. Other patients tested were those with chronic urticaria/angioedema (as well as other less common conditions described in the Results) who were not considered likely to have IgE-mediated FA but where testing was undertaken for purposes of patient reassurance. Following descriptions of a possible relationship between tick bites and adult onset red meat allergy (20, 21), tick bite reactive patients were also tested.

Diagnostic criteria

Sensitization was defined as the presence of a positive SPT or IDT. IgE-mediated FA was diagnosed only if there was also a history of acute systemic allergic reaction (one or more of urticaria, vomiting, bronchospasm or vascular collapse) following known allergen exposure,

combined with a positive SPT or IDT to the relevant allergen. The severity of systemic allergic reactions was classified as described by Brown (23) - mild (skin and subcutaneous tissue involvement only), moderate (features suggestive of respiratory, cardiovascular or gastrointestinal involvement: dyspnea, wheeze, chest or throat tightness, nausea, vomiting, abdominal pain, dizziness, sweating) or severe (cyanosis, hypotension, confusion, collapse, loss of consciousness, incontinence). A diagnosis of anaphylaxis was assigned if either of the first two criteria of the 2005 National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium definition were fulfilled (24). For the purposes of this study, red meat was defined as beef, lamb, pork, horse or kangaroo, and red meat allergy was diagnosed when one or more was considered to be the cause of FA.

In vitro testing

Sera were aliquoted and stored at -5°C in the ACT until February 2011, then transported on dry ice to the University of Virginia and stored at -20°C until analysis. Total and specific IgE antibodies were measured by using either commercially available ImmunoCAP (Phadia US, Portage, Mich, USA) or a modification of the assay with streptavidin on the solid phase as previously described (19, 25). The assays were performed with the ImmunoCAP 250 instrument, and the results were expressed as international units per milliliter, with the international unit both for specific and total IgE being approximately 2.4 ng. A positive anti-alpha-Gal specific assay was defined as >0.35 IU/mL. IgE antibodies to alpha-Gal were measured by streptavidin CAP technique, by adding approximately 5 µg biotinylated antigen to each CAP before adding 40 µL undiluted serum. IgE antibodies to beef (f27), pork (f26), lamb (f88) and bovine gelatin (c74) were measured using commercially available assays.

Detection of alpha-Gal in gelatin and bovine products

The concentrations of alpha-Gal in bovine-derived gelatin colloids (Gelofusine & Haemacel), whipped cream (ultra-pasteurized whipped cream), cow's milk and beef thyroglobulin (Sigma-Aldrich) were measured using a modified inhibition radioimmunoassay (RIA) (19). Cetuximab (ImClone Systems and Bristol-Myers Squibb, New York and Princeton, New Jersey) and fish-derived gelatin were included as positive and negative controls, respectively, as cetuximab is known to contain alpha-Gal (26) and fish gelatin is not known to cross-react with mammalian gelatin (27). One gram samples of gelatin colloid, whipped cream, cow's milk, beef thyroglobulin or fish gelatin and 5mg of cetuximab were each incubated for two hours with a dilution of serum from a subject with known high titer IgG antibodies to alpha-Gal. A standard curve was created using serial dilutions of the linear trisaccharide Gal α 1-3Gal β 1-4GlcNAc (V-Labs, Inc, Covington, LA) (online Figure e1). I¹²⁵ radiolabeled Gal α 1-3Gal β 1-4GlcNAc-BSA (V-Labs, Inc, Covington, LA) was then added and incubated at room temperature for two hours. Finally, goat anti-human IgG (Strategic Biosolutions, Newark, DE) was added as a precipitating antibody and stored overnight at 4°C, followed by washing of precipitates in PBS three times and measurement of radioactivity with a gamma counter (Perkin Elmer, Waltham, MA).

Challenge procedures

When clinically indicated, open oral challenges with food grade gelatin confectionary were performed under medical supervision, until a total of ~10gm oral gelatin was consumed, followed by a 3 hour wait after the last dose was consumed. Intravenous challenges were performed in an intensive care unit using either Haemacel or Gelofusine (35 or 40 mg/ml gelatin, respectively), according to product availability in the challenge hospital. Infusions of a 1/10 dilution of colloid in normal saline, initially 1 ml/minute, were doubled every 5

minutes. Once 8 ml/minute was reached, the protocol was restarted using undiluted colloid. When reactions occurred, patients were observed for an additional 4 hours after symptom resolution.

Statistical analysis

We compared quantitative measures of IgE to alpha-Gal and the presence or absence of positive gelatin skin tests with the risk of anaphylaxis using unpaired t tests. The relationships between anti-alpha-Gal IgE levels and speed of symptom onset as well as gelatin IDT wheal size were examined by calculating Pearson correlation coefficients. Allergen specific levels <0.35 or > 100 KU/L were treated as 0.35 or 100, respectively for these calculations. A two-sided *P* value <0.05 was considered statistically significance. Statistical analyses were performed with SPSS software, version 18.0 (SPSS, Inc, Chicago, Ill), and GraphPad Prism, version 4 (GraphPad Software, Inc, La Jolla, Calif).

RESULTS

Patient characteristics

Between 1995 and 2011, 1159 adults assessed by the first author (RJM) aged 18 to 101 years (423 male) were diagnosed with FA, triggered by seafood (n=284 patients), peanut (n=189), tree nuts (n=188), systemic allergic reactions to fruit/vegetables (n=134), wheat (n=77), egg (n=57), red meat (n=40), sesame seed (n=22), cow's milk (n=21) or soybean (n=8). Of 40 red meat allergics identified, 18 (46%) were male aged 18-78 years (median 48) and 27 had anaphylaxis. Patients estimated symptom onset between 15 minutes and 9 hours after ingestion (median 3 hours) with significantly delayed onset associated with nocturnal episodes after the evening meal. Ten were sensitized to red meat only (M) and 30 to red meat and gelatin (MG) on allergy testing. There was no relationship between onset time and likelihood of anaphylaxis (*P*=0.88) or gelatin sensitization and likelihood of anaphylaxis (*P*=0.13). With the exception of two vegetarians (MG1, MG26), most patients diagnosed with red meat allergy reported tolerance on other occasions.

Meat and gelatin co-sensitization and co-reactivity

32 patients were co-sensitized to red meat and gelatin, including two patients with intraoperative gelatin colloid anaphylaxis who were red meat tolerant (GC 1 and 2) and 29 patients diagnosed with red meat allergy (MG 1-29; Table 1). Of this MG group, 12 reported anaphylaxis when red meat was not ingested, including two additional patients with intraoperative gelatin colloid anaphylaxis prior to presentation with red meat allergy (MG22 and MG24; 5). One additional patient (MG12) with recurrent red meat anaphylaxis remained well for five years on a meat/gelatin-free diet. Despite wearing a MedicAlert bracelet to warn of her possible gelatin allergy, she was given 40ml of intravenous Gelosfusine (~1.6gm gelatin) following a myocardial infarction and developed urticaria, bronchospasm, hypoxia and hypotension (hospital records verified by the first author, RJM; Table 1). Nine additional patients reported systemic reactions following oral gelatin consumption on separate occasions (e.g. desserts) where meat ingestion was denied.

Prospective evaluation of gelatin sensitization

Between 1997 and 2011, 1335 individuals underwent gelatin IDT. Positive results were observed in 40 (2.8%) individuals: 30/40 (75%) diagnosed with red meat allergy (M+MG); 2/2 patients with gelatin colloid anaphylaxis (co-sensitized to meat and gelatin but meat tolerant clinically; GC), 4/172 (2.3%) with idiopathic anaphylaxis (ID) and 5/1121 (0.4%) others tested without suspected meat/gelatin allergy (Tables 1, 2). Sensitization to gelatin was titratable in all patient groups (Figure 1). Five years after evaluation for possible insect

venom allergy, however, one normally vegetarian subject with a positive gelatin test of unknown significance returned following meat anaphylaxis, was sensitised to red meat and gelatin on testing and reclassified in the MG group (MG26).

Gelatin challenges

In the four cases classified as idiopathic anaphylaxis assessed 2001-2003 (but with with positive gelatin tests), red meat was implicated historically on multiple occasions but sensitization to red meat could not be demonstrated on SPT; meat IDT was not undertaken at the time until reports of its utility (19). Since removal of dietary meat was undesirable without further evidence, all agreed to an oral challenge with gelatin and if negative, with IV gelatin colloid. While all tolerated a supervised oral challenge with 10gm gelatin, each developed urticaria and bronchospasm with intravenous gelatin colloid challenge at doses of 1.2gm (ID1; online Figure e2), 0.1gm (ID2), 0.024gm (ID3) and 4.1gm (ID4). Avoidance of red meat and gelatin has been reduced patient reported episodes on followup from 1 episode in 6 months to 1 episode in 8 years (ID1), from 10 episodes/year to none in 6 years (ID2), from 3 episodes in 2 months to none in 6 years (ID3) and from 5 episodes/year to none in 5 years (ID4).

Additional in vitro testing

Where available, sera were tested for allergen specific IgE to meat, gelatin and alpha-Gal (Table 3). In the M/MG groups, 23/26 were sensitised to one or more red meat, 20/24 to alpha-Gal (plus 2 borderline results) but only 1/25 to gelatin despite positive gelatin IDT in 20 of these patients (Table 3). There was no association between anti-alpha-Gal IgE and likelihood of anaphylaxis and only a weak inverse relationship ($r=0.37$; $P=0.074$) between time of onset and anti-alpha-Gal IgE. There was a strong correlation between anti-alpha-Gal IgE and positive gelatin IDT reactivity: of 22 IgE alpha-Gal positive sera from the M, MG, ID and G groups, 20 had positive gelatin skin tests. Of 22 with positive gelatin IDT, 20 were anti-alpha-Gal IgE positive. Furthermore, there was a correlation between mean gelatin IDT wheal diameter and in vitro IgE levels to alpha-Gal ($r=0.46$; $P<0.01$),

Comparison of testing methods

Where positive, the results of beef and pork SPT and IDT suggested sensitization to both (data not shown). Of 40 patients diagnosed with red meat allergy (M+MG), meat SPT was positive in 26/40 (65%), meat IDT positive in 18/18 (100%), gelatin IDT positive in 30/40 (75%), meat Immuncap positive in 23/26 (88%) and anti-alpha-Gal IgE in 25/26 (96%).

Detection of alpha-Gal in gelatin and bovine products

Given the positive correlation between the results of gelatin skin testing and anti- alpha-Gal IgE, we examined whether alpha-Gal might be detectable in gelatin, using a sensitive RIA (10). Alpha-Gal was detected in both gelatin colloids: $0.52\mu\text{g} \pm 0.1\mu\text{g}$ of alpha-Gal/gm of Gelofusine and $0.44\mu\text{g} \pm 0.2\mu\text{g/gm}$ of Haemaccel). Using similar techniques, the concentrations of alpha-Gal were $5.6\mu\text{g}$ of alpha-Gal per gram of beef thyroglobulin and $1.4\mu\text{g} / \text{g}$ of heavy cream. By contrast, no detectable alpha-Gal was found in cow's milk (skim, 1% or 2% milk fat). Of the 21 oligosaccharides identified on cetuximab, approx 30% have one or more alpha-1,3 linked galactosyl residues as measured by peak area on TOF-MS spectra (28) and alpha-Gal was detected at a concentration of $10.2\mu\text{g} / 5\text{mg}$ of cetuximab in the inhibition RIA. By contrast, alpha-Gal was undetectable in fish gelatin (lower limit of assay = $0.01\mu\text{g}$).

Relationship between red meat allergy and tick exposure

When questioned about exposure to (and adverse reactions from) tick bites, 24/40 meat-allergics described large local bite reactions and 26 lived in (or visited) tick-endemic areas. Conversely, of 10 tick allergic patients evaluated (6 with tick anaphylaxis, none with FA), 7/10 were sensitised to red meat on skin and/or in vitro testing, 3/7 tested were sensitised to gelatin on IDT and 7/9 had serum anti- alpha-Gal IgE (Table 4).

DISCUSSION

We have identified a significant relationship between adult onset red meat allergy and sensitization and clinical reactivity to gelatin, supported by the results of intraoperative exposure (MG23, 24; GC1,2), accidental exposure (MG12), observed challenge (ID1-4) or claims of reactivity to oral gelatin. Consistent with previous studies, SPT reactivity using commercial meat extracts were relatively small and sometimes negative (19, 29), and IDT and in vitro testing were more sensitive at detecting sensitization (19, 30). In most cases, symptom onset was delayed for a median of 3 hours after ingestion; most were sensitised to alpha-Gal; and there was a historical association between tick bite exposure, sensitization and allergy to red meat (20, 21). While beef was the dominant meat triggering symptoms, this may reflect non allergic factors such as cost, availability, the amount consumed at any one sitting as well as popularity: beef consumption accounts for more than the sum total of all other meat consumed in Australia (31).

There are some caveats to be considered in interpreting our study. First, we specifically studied only adults with red meat allergy (due to the potential discomfort from IDT) and so our results cannot necessarily be extrapolated to children, although in vitro gelatin sensitization has been reported in children with red meat allergy (32). Second, we were only able to examine some patients repeatedly as the study developed over 14 years and as a consequence, sera for in vitro analysis were only available from a subset. While acknowledging that claims of reactions to oral gelatin (without meat) in 9 MG patients is dependent on patient reports, it is difficult to ignore the clinical significance of a positive gelatin IDT at least as a risk factor for gelatin colloid reactivity (as described above), including one case of accidental exposure where the risk was identified prospectively (MG12). Conversely, clinical reactivity to red meat was observed in 2/4 colloid-allergic patients and gelatin sensitization was predictive of red meat allergy in one “healthy control” (MG26). While the significance of gelatin sensitization in four otherwise healthy subjects with drug allergy, meat sensitization in two patients with gelatin colloid allergy and gelatin/meat sensitization in patients evaluated for tick bite allergy remains currently uncertain, this may become apparent with further observation (e.g. MG26) or may represent sensitization without clinical allergy, as recently reviewed (33). While we would have preferred to undertake more gelatin challenges in patients with a positive gelatin test, our ability to do so was constrained by patient age, co-morbidity, patient unwillingness to do so and geographical location (most lived at the coast > 200km from the inland clinical practice),

Most reports of serious allergic reactions to gelatin implicate parenteral exposure, either to gelatin colloids used as plasma expanders or to gelatin-containing vaccines. Since 1999, 129 reports of anaphylaxis (including 2 deaths) have been associated with colloid use in Australia, with colloid the only suspected trigger in 58 cases (Rob Crowdy, Australian Therapeutic Good Administration, personal communication December 2011). Both IgE-independent and -dependent mechanisms have been proposed to play a role in reactions to gelatin colloids. Evidence in favor of the former includes activation of kinin pathways and histamine release in healthy volunteers (34). That at least some reactions to gelatin colloids are IgE-mediated, however, is supported by the correlation between skin test reactivity and clinical reactions in this series as well as evidence of immunological cross-reactivity

between gelatin and gelatin-derived colloids (8, 10). These data are further strengthened by evidence that 1) allergic reactions to gelatin-containing vaccines are also IgE-mediated; 2) IgE is directed against the alpha 2 chain of type I collagen; 3) reactions are more common in patients with prior exposure to gelatin-containing vaccines; 4) reactions are uncommon if gelatin is extensively hydrolysed; and, 5) patients generally require parenteral exposure to trigger sensitization (12, 35). Vaccine-reactive patients (7, 11, 12; sometimes also reactive to oral gelatin), however, are likely to be more sensitive to gelatin than our patients, with sensitization detectable by SPT using diluted vaccines (~0.2mg/ml gelatin vs. ~ 40mg/ml gelatin IDT in our patients) and reactivity to approximately 2mg parenteral gelatin (36), compared to 24 to 4100 mg in our challenge patients.

While our data are consistent with gelatin sensitization being a risk factor for gelatin colloid allergy, a relevant issue is whether sensitization also conveys a significant risk of clinical reactivity to oral gelatin and, by implication, the need for ongoing dietary restrictions. Eluted when meat is cooked and cooled, gelatin is present in some confectionery (e.g. marshmallows), food thickeners, dips, glazes and icing and act as a fat substitute in yoghurt, mayonnaise and ice cream (9). Gelatin can be found in sausage coatings, salami, tinned hams, pâté and meat stock, and used to clarify fruit juice and wine (9). Gelatin can thus be considered a potential occult food allergen as exposure is ubiquitous, and the method of extraction (acid and alkaline hydrolysis with heat treatment) make it more likely to survive food preparation than heat-labile meat proteins such as bovine gamma globulin and bovine serum albumin (3).

That reactions to topical or oral gelatin can occur is supported by rare case reports of allergic reactions to “hydrolysed protein” (gelatin) in shampoo, collagen implants, “catgut” sutures, collagen-derived contact lenses, as well as to gelatin present as binding agent in tablets, capsules, suppositories or confectionary (4, 6, 9, 37-40). While sensitization alone is not equivalent to being clinically allergic (41), 9 of our patients reported systemic allergic reactions (including anaphylaxis) after ingestion of gelatin containing food without red meat. While these claims (and the scarcity of published cases) may reflect poor recognition of gelatin as a possible trigger, episodes erroneously labelled as being idiopathic (due to negative routine allergy tests), the absence of co-factors, or a higher risk from parenteral exposure, one potential clue may be the oral dose required to trigger an allergic reaction. Our challenge patients failed to react to 10gm of oral gelatin, in retrospect a relatively small dose compared to the large amount intravenously required to trigger anaphylaxis in the same individuals. While ongoing studies await the results of challenges using higher doses of oral gelatin, our clinical practice in the meantime has been to advise patients with red meat allergy *and* gelatin sensitization to be cautious about ingesting substantial quantities and to wear a MedicAlert bracelet warning of potential risk from gelatin colloid exposure, a prudent approach that did not protect one patient in our series.

Consistent with previous studies (19, 30), in vitro testing appeared to be more sensitive at detecting sensitization to meat derived allergen than skin testing, with wheal sizes using commercial meat extracts being relatively small or negative and requiring IDT to detect sensitization (Table 1). Explanations for this have been discussed previously (19), including the possibility that folding of proteins within extracts might make alpha-Gal less available for mast cell cross-linking, that antibodies to uncharged carbohydrate molecules like alpha-Gal might be of low affinity (42), or perhaps of specific relevance, evidence that alpha-Gal concentration is lower in commercial meat extracts than in crude extracts of real meat (19), perhaps accounting for lower sensitivity.

In this context, it is perhaps not surprising that IDT was more sensitive at detecting gelatin sensitization yet paradoxically in vitro testing was negative in almost all samples. This

cannot be explained by serum sample degradation due to prolonged storage, since IgE to meat and alpha-Gal was detected in parallel assays. Potential explanations include assay insensitivity due to the preparation of gelatin required for immunoassay grade stability or if alpha-Gal is the allergenic target, insufficient concentration on the ImmunoCap to detect sensitization. Alternatively, gelatin-reactive IgE may be of low affinity or low concentration (as previously suggested for anti-cross-reactive carbohydrate determinants IgE antibody; 42). Regardless of the explanation, the relative insensitivity of current commercial in vitro assays for gelatin IgE is underlined by negative results even in patients with demonstrated anaphylaxis to gelatin colloid challenge.

Our data thus supports the use of gelatin colloids where possible (not available in the USA at this time) as useful reagents for skin testing to confirm suspected gelatin allergy, and as less sensitive (but still useful) reagents to detect suspected red meat allergy, with a positive test having potential clinical relevance for avoidance strategies. While the option of using food-grade gelatin for testing may be considered in patients with suspected meat and/or gelatin allergy, the potential for processing of food-grade gelatin to yield extracts of varying molecular weights may limit its use as a testing reagent and might also explain inconsistent clinical responses to oral exposure and inconsistent in vitro assays to gelatin, as previously reported (11). While comparison of results using gelatin colloid and crude gelatin extracts for SPT/IDT merits future study, our plan to undertake IDT in >1000 patients led us to not consider using an unstandardized and non-sterile reagent for our *prospective* study in a large number of individuals in whom meat/gelatin allergy was unlikely to be present.

It is likely that allergic responses to red meat are heterogeneous, with some responses directed towards heat labile meat proteins (3), others directed towards alpha-Gal and others to gelatin. Consistent with previous studies (43, 44), the majority of our patients experienced only occasional overt reactions despite regular meat consumption. Potential explanations remain speculative, but may include the absence of co-factors (e.g. exercise), the amount ingested (other studies suggest that >75gm is generally required to trigger symptoms; 44), the way in which meat is prepared (influencing the quantity and number of allergens eluted or presence of additional heat-labile allergens) or perhaps fat content. Moreover, observations that sIgE anti- alpha-gal may decrease naturally over time without additional tick bites (Platts-Mills & Commins, unpublished observations) may account in part for varying degrees of tolerance over time. The likelihood of consumption of larger amounts of meat in the evening raises the possibility that circadian changes in gut motility (45) may influence allergen absorption. Furthermore, nocturnal onset while asleep may prevent recognition of milder reactions and delay recognition of more severe episodes, perhaps accounting for some considerable delays observed (e.g. patient MG18).

We were also able to confirm previous Australian and USA reports of an association between adult onset red meat allergy, alpha-Gal sensitization and a history of tick bite reactions (19-21), which may explain the geographical location of most of our patients. This is significant because we also found asymptomatic sensitization to gelatin, meat and alpha-Gal in a small number of patients with tick bite reactions in a different country with different tick species. The detection of alpha-Gal in gelatin preparations and the correlation between sensitization to red meat, gelatin and alpha-Gal in most cases raises one intriguing possibility: that as has been proposed for reactions to cetuximab (46), clinical reactivity to gelatin might in some cases be mediated by anti- alpha-Gal IgE. If so, this might in part help explain the poor correlation between the results of in vitro and IDT testing to gelatin in our adult population compared to younger and more sensitive patients reacting to lower doses of gelatin in vaccines (7, 11, 12) with IDT testing acting as an indirect marker of IgE reactivity to alpha-Gal, and with positive in vitro testing results in the vaccines studies perhaps reflecting either IgE to other gelatin moieties or patients with very high titers of anti-gelatin

IgE. Of interest, if tick bite exposure is a risk factor for meat/gelatin sensitization (and precedents for geographical variation in anaphylaxis have been described; 26), then one might reasonably expect that adverse reactions to gelatin colloid might also follow a similar pattern. Unfortunately, the level of detail available in Australian adverse drug reports precludes such analysis (Nick Simpson, Australian Therapeutic Goods Administration, personal communication January 2012).

In conclusion, we found that most patients allergic to red meat are sensitized to gelatin, and that a subset will report reactions to IV (and sometimes oral gelatin) as well. Gelatin sensitization poses a risk of clinical reactivity to both red meat and gelatin, albeit not in all patients. Patients presenting with clinical reactions to either trigger thus merit evaluation for sensitization to both triggers and warned appropriately if results are positive. Taking into account the relationship between the results of gelatin and alpha-Gal testing in our patients, and the detection of alpha-Gal in gelatin, a positive test to either may also represent a risk factor for both meat, and gelatin allergy. As the syndrome of delayed anaphylaxis to mammalian meat highlights, correct diagnosis is hampered by delayed onset, inconsistent ability to tolerate the food on some occasions, the inability of patients to always correctly identify their dietary triggers and geographical limitations in the availability of diagnostic tests for anti-alpha-Gal and anti-gelatin IgE. Future challenges include determining whether a salivary component common to multiple tick species from different continents may be the sensitizing agent (21) and the factors contributing to delayed onset of symptoms to red meat compared to other foods.

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ABBREVIATIONS

ACT	Australian Capital Territory
alpha-Gal	galactose-alpha-1,3-galactose
FA	Food allergy
G	Gelatin
GC	Gelatin colloid
ID	Idiopathic
IDT	Intradermal testing
M	Meat
MG	Meat Gelatin
RIA	Radioimmunoassay
SPT	Skin prick testing

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Key messages

- Most patients allergic to red meat are sensitized to gelatin and a subset will be clinically allergic to both.
- The detection of alpha-Gal in gelatin and correlation between the results of alpha-Gal and gelatin testing raises the possibility that alpha-Gal IgE may be the target of reactivity to gelatin.
- The relationship between tick bite reactions in meat-allergic subjects and meat sensitization in patients with tick bite allergy is suggestive of a possible role for tick bites in meat allergy pathogenesis.

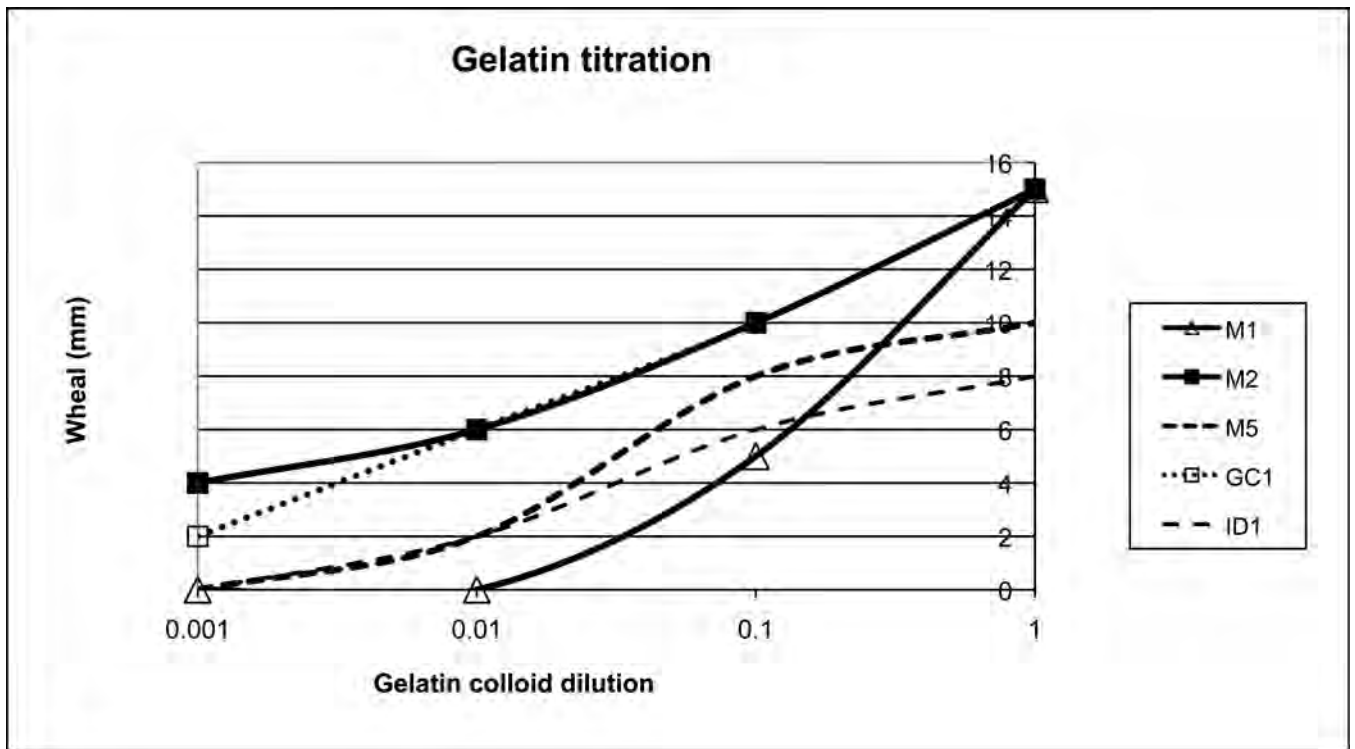


Figure 1. Titration of intradermal gelatin colloid skin testing

Intradermal testing with gelatin colloid was titrated in 17 cases, with positive tests detectable at dilutions of undiluted colloid only (3 patients), 1/10 (6 patients), 1/100 (8 patients) and 1/1000 (0 patients). Representative examples are shown.

Table 1

Clinical characteristics of patients diagnosed with red meat or gelatin allergy and other patient groups, as assessed by skin testing.

Patient group	Gender	Age (years)	Trigger(s) of clinical reactivity	Onset (hrs)	Severity	Anaphylaxis	Meat Test (SPT/IDT wheal size in mm)	Gelatin Test (SPT/IDT wheal size in mm)	No. episodes (time period)
Meat									
M1	M	37	B	2	moderate	Yes	6/nd	0/0	3 (3 weeks)
M2	M	59	B	0.5	severe	Yes	4/nd	0/0	2 (6 months)
M3	F	32	B, L, P	2	moderate	No	4/6	0/0	"all life" > 4/yr
M4	F	25	P	2	moderate	Yes	0/4	0/0	"all life" > 4/yr
M5	M	18	B	2	moderate	No	3/nd	0/0	"all life" > 4/yr
M6	F	56	B, P	2	moderate	Yes	3/nd	0/0	2 (6 months)
M7	M	50	H	3	moderate	Yes	3/6	0/0	"all life" > 4/yr
M8	F	31	B, L	0.5	moderate	No	5/nd	0/0	1 (10 yrs ago)
M9	M	36	B	3	moderate	Yes	3/nd	0/0	10 (6 months)
M10	F	23	B, P	2	moderate	No	5/nd	0/0	2 (3 months)
Meat + Gelatin									
MG1	M	77	B	6	moderate	Yes	3/15	0/15	2 (2 months)
MG2	M	51	B, L, G	5	severe	Yes	3/nd	0/15	10 (8 months)
MG3	F	28	B, L, K	1.5	moderate	Yes	0/14	0/12	>25 (6 yrs)
MG4	F	21	B	3	moderate	Yes	0/8	0/8	2 (2 months)
MG5	M	64	B	3	severe	Yes	0/12	0/12	>10 (4 yrs)
MG6	F	18	P	6	moderate	Yes	6/10	0/8	"all life" > 4/yr
MG7	M	52	B, G	6	mild	No	3/10	0/12	3 (3 months)
MG8	F	16	B	6	moderate	No	0/8	0/6	1 (2 months)
MG9	M	78	B	8	severe	Yes	0/10	0/15	6 (3 yrs)
MG10	F	60	L	2	moderate	No	4/10	0/10	1 (2 months)
MG11	M	52	B, L, G	5	moderate	Yes	3/nd	0/15	4 (18 months)
MG12	F	71	B	3.5	severe	Yes	3/nd	0/12	>20 (2 yrs)
MG13	F	51	B, L, P, G	0.25	severe	Yes	3/nd	2/12	> 10 (2 yrs)
MG14	F	28	L, K	1.5	severe	Yes	5/nd	0/12	3 (3 months)
MG15	F	73	B	4	mild	No	3/nd	0/10	3 (5 yrs)

Patient group	Gender	Age (years)	Trigger(s) of clinical reactivity	Onset (hrs)	Severity	Anaphylaxis	Meat Test (SPT/IDT wheal size in mm)	Gelatin Test (SPT/IDT wheal size in mm)	No. episodes (time period)
MG16	F	63	B, GC,	2	severe	Yes	3/nd	0/5	> 50 (10 yrs)
MG17	F	35	B, L, P, G	0.25	severe	Yes	3/nd	0/15	2 (8 months)
MG18	M	44	B	9*	moderate	Yes	0/15	0/12	2 (6 months)
MG19	F	27	B	2	mild	No	3/nd	0/10	1 (6 months)
MG20	M	46	B, L	6	severe	Yes	3/nd	0/12	5 (3 yrs)
MG21	F	48	B, P	8	mild	No	3/nd	0/6	>5 (5 yrs)
MG22	M	69	B, GC, G	6	severe	Yes	3/nd	3/10	>10 (3 yrs)
MG23	M	66	B, L, P, GC	7	severe	Yes	3/nd	0/12	>30 (4 yrs)
MG24	M	72	GC, G, P	0.5	severe	Yes	3/nd	0/5	2 (6 months)
MG25	F	41	G, P	2	mild	No	3/nd	3/10	4 (2 yrs)
MG26	F	39	B	7	mild	No	0/10	0/10	2 (6 months)
MG27	M	74	B, L	3	severe	Yes	0/15	0/15	18 (1 yr)
MG28	F	61	B, L, G	4	severe	Yes	0/12	0/12	8 (2 yrs)
MG29	M	19	B, P	4	severe	Yes	0/12	0/12	1 (1 month)
MG30	F	65	B, L	1	moderate	No	2/10	0/12	6 (10 yrs)
Gelatin Colloid									
GC1	M	77	GC	0.5	severe	Yes	0/4	0/15	1
GC2	M	63	GC	0.5	moderate	Yes	0/10	0/8	1
Idiopathic									
ID1	F	33	P	0.25	moderate	Yes	0/nd	0/5	1 (6 months)
ID2	F	22	B	2	moderate	No	0/nd	0/7	5 (1 yr)
ID3	F	35	B, P	5	moderate	Yes	0/nd	0/6	3 (2 months)
ID4	F	54	B, L	3	severe	Yes	0/nd	0/8	>20 (3 yrs)
Drug Allergy									
D1	F	35	n/a	n/a	n/a	n/a	nd/nd	nd/5	n/a
D2	M	64	n/a	n/a	n/a	n/a	nd/nd	nd/12	n/a
D3	F	37	n/a	n/a	n/a	n/a	nd/nd	nd/5	n/a
D4	F	20	n/a	n/a	n/a	n/a	nd/nd	nd/7	n/a

Patients diagnosed with allergy to red meat and/or gelatin as well as control groups underwent skin prick testing (SPT) or intradermal testing (IDT) using meat-derived allergen and gelatin colloid. IDT was normally only undertaken if SPT was negative. Results are described as mean wheal diameter in mm or not done (nd) as indicated. For the purposes of this study, red meat was defined as beef (B), pork (P),

lamb (L) horse (H) or kangaroo (K). Other patients were clinically allergic to oral gelatin (G) or gelatin colloid (GC). The time of symptoms onset after meals was a patient estimate, with one patient (MG18) reporting symptoms after 6 hours on one occasion and 9 hours after another.

Table 2**Gelatin sensitisation**

1335 patients underwent intradermal testing with gelatin colloid between 1997 and 2011.

Clinical group	+ve tests	No. tested	% +ve
Red meat	30	40	75
Gelatin colloid	2	2	100
Venom allergy	1*	242*	0.4
Idiopathic anaphylaxis	4	172	2.3
Drug allergy	4	368	1.1
Non-meat food allergy	0	222	0
Miscellaneous	0	290	0
Idiopathic angioedema	0	81	
Eosinophilic esophagitis	0	79	
Chronic urticaria	0	77	
Irritable bowel syndrome	0	24	
Anxiety disorder	0	12	
ACE inhibitor angioedema	0	8	
Laryngospasm	0	6	
Animal allergy	0	2	
Semen allergy	0	1	
Total	40*	1335	2.9

* One patient returned with red meat anaphylaxis 5 years after investigation for insect venom allergy and was reclassified in the red meat allergy group.

Table 3

In vitro testing in patients diagnosed with allergy to red meat or gelatin

Patient group	Pork (f26)	Beef (f27)	Lamb (f88)	Alpha-gal	Gelatin (c74)
Meat					
M1	7.08	13.7	5.68	2.08	<0.35
M2	0.07	0.07	0.04	0.35	<0.35
M3	0.02	0.06	0.1	0.35	<0.35
M6	0.42	0.73	0.21	0.97	<0.35
Meat + Gelatin					
MG1	16.9	35.1	15.3	93	<0.35
MG2	17.1	29.2	10	64.2	<0.35
MG3	6.43	8.25	4.4	12.4	<0.35
MG4	0.81	1.18	0.59	2.63	<0.35
MG5	18.3	37.1	<0.10	66.9	<0.35
MG6	1.28	0.38	1.18	<0.35	<0.35
MG7	17.7	34.8	12.7	100	<0.35
MG8	1.36	1.62	1.41	3.56	<0.35
MG9	2.54	3.7	<0.35	7.9	<0.35
MG10	0.82	1.74	<0.35	12.6	nd
MG11	0.75	0.88	1.15	3.91	<0.35
MG12	0.79	1.39	0.66	2.23	<0.35
MG13	5.39	5.64	5.91	6.09	<0.35
MG14	15.7	17.9	16.6	20.7	0.42
MG15	0.37	0.41	0.31	1.22	<0.35
MG16	0.58	1.04	0.6	2.59	<0.35
MG17	0.04	0.17	0.18	0.35	<0.35
MG26	2.64	4.73	5.68	9.91	<0.35
MG27	11.4	13.7	7.68	45.2	<0.35
MG28	4.62	6.16	3.17	11.5	<0.35
MG29	13.6	14.6	10.3	29.5	<0.35
MG30	17.4	27.1	11.8	>100	<0.35
Idiopathic					

Patient group	Pork (f26)	Beef (f27)	Lamb (f88)	Alpha-gal	Gelatin (c74)
ID3	0.04	0.05	0.02	0.35	<0.35
Gelatin colloid					
G1	<0.35	0.42	<0.35	1.54	<0.35

IgE to meat, alpha-Gal and gelatin was measured by ImmunoCap in patients diagnosed as being allergic and sensitised to meat only (M), to meat and gelatin (MG), to gelatin colloid (GC) and in one patient classified with idiopathic anaphylaxis (ID). An allergen-reactive IgE of ≥ 0.35 KU/L was considered to be positive. nd = not done.

Table 4

Characteristics of tick allergic subjects

Patient	Gender	Age (years)	Severity of tick reactions	Meat test (SPT/IDT wheal size in mm)	Gelatin test (SPT/IDT wheal size in mm)	Pork (I26)	Beef (I27)	Lamb (I88)	Alpha-gal	Gelatin (c74)
T1	F	65	Local	0/12	0/12	25.7	46.6	nd	100	<0.35
T2	F	66	Local	0/8	0/0	<0.35	0.61	<0.35	2.28	<0.35
T3	M	22	Local	0/7	0/7	3.17	3.82	1.82	6.57	<0.35
T4	M	67	Anaphylaxis	5/8	0/0	0.74	1.42	<0.35	2.95	<0.35
T5	F	82	Anaphylaxis	0/0	0/0	<0.35	<0.35	<0.35	<0.35	<0.35
T6	F	68	Anaphylaxis	0/nd	nd/nd	<0.35	<0.35	<0.35	0.72	<0.35
T7	M	63	Anaphylaxis	0/nd	nd/nd	<0.35	<0.35	<0.35	0.35	<0.35
T8	M	70	Anaphylaxis	nd/nd	0/0	<0.35	0.75	<0.35	5.74	<0.35
T9	F	67	Anaphylaxis	nd/nd	nd/nd	0.36	0.76	0.36	2.49	<0.35
T10	F	51	Local	0/10	0/6	0.61	1.01	0.57	nd	<0.35

IgE to meat, gelatin and alpha-Gal was measured in patients reporting allergic reactions to tick bites but without known food allergy. The results of skin prick tests (SPT) or intradermal tests (IDT) are shown (mean wheal size in mm) are shown, with results ≥ 3 mm than the negative control defined as positive. IgE to meat, alpha-Gal and gelatin was measured by ImmunoCap with levels > 0.35 KU/L considered to be positive. nd = not done.

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Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose- α -1,3-Galactose

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Abstract

BACKGROUND—Cetuximab, a chimeric mouse–human IgG1 monoclonal antibody against the epidermal growth factor receptor, is approved for use in colorectal cancer and squamous-cell carcinoma of the head and neck. A high prevalence of hypersensitivity reactions to cetuximab has been reported in some areas of the United States.

METHODS—We analyzed serum samples from four groups of subjects for IgE antibodies against cetuximab: pretreatment samples from 76 case subjects who had been treated with cetuximab at multiple centers, predominantly in Tennessee, Arkansas, and North Carolina; samples from 72 control subjects in Tennessee; samples from 49 control subjects with cancer in northern California; and samples from 341 female control subjects in Boston.

RESULTS—Among 76 cetuximab-treated subjects, 25 had a hypersensitivity reaction to the drug. IgE antibodies against cetuximab were found in pretreatment samples from 17 of these subjects; only 1 of 51 subjects who did not have a hypersensitivity reaction had such antibodies ($P < 0.001$). IgE antibodies against cetuximab were found in 15 of 72 samples (20.8%) from control subjects in Tennessee, in 3 of 49 samples (6.1%) from northern California, and in 2 of 341 samples (0.6%) from Boston. The IgE antibodies were shown to be specific for an oligosaccharide, galactose- α -1,3-galactose, which is present on the Fab portion of the cetuximab heavy chain.

CONCLUSIONS—In most subjects who had a hypersensitivity reaction to cetuximab, IgE antibodies against cetuximab were present in serum before therapy. The antibodies were specific for galactose- α -1,3-galactose.

RECOMBINANT MONOCLONAL ANTIBODIES have an increasing role in the treatment of cancers, inflammatory bowel disease, rheumatoid arthritis, and asthma.¹⁻³ These agents can cause rapidly developing, severe hypersensitivity reactions.⁴⁻⁷ Cetuximab (Erbix, Bristol-Myers Squibb and ImClone Systems), a chimeric mouse–human IgG₁ monoclonal antibody

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against the epidermal growth factor receptor (EGFR), is approved for use in metastatic colorectal cancer and squamous-cell carcinoma of the head and neck.^{2,6,8-10} According to the drug's product label, severe hypersensitivity reactions to cetuximab occur in 3% of patients. However, higher rates and clusters of cases have been reported in North Carolina, Arkansas, Missouri, Virginia, and Tennessee.^{6,9,11} A recent study showed that 22% of patients who were treated with cetuximab in Tennessee and North Carolina had severe hypersensitivity reactions.¹¹ In contrast, rates of hypersensitivity reactions were lower (<1%) in most centers in the Northeast.¹¹ A review of case reports on hypersensitivity reactions to cetuximab revealed that many such reactions occurred within minutes after the patient's first exposure to the drug and were compatible with IgE-mediated anaphylaxis.¹¹⁻¹³

We investigated the hypothesis that severe hypersensitivity reactions occurring during the initial infusion of cetuximab are mediated by preexisting IgE antibodies against cetuximab. Using a recently developed assay,¹⁴ we found such IgE antibodies in serum samples from case subjects and control subjects. Our results indicate that these antibodies, which are present before treatment, are a cause of severe hypersensitivity reactions to cetuximab. The antibodies are specific for an oligosaccharide, galactose- α -1,3-galactose, which is present on the Fab portion of the cetuximab heavy chain. Such IgE antibodies also bind to a range of mammalian proteins, a finding that is consistent with the expression of galactose- α -1,3-galactose on proteins from most nonprimate mammals. We also found that there is a high prevalence of the IgE antibody in areas of the United States where anaphylactic reactions to cetuximab have occurred.

METHODS

STUDY SUBJECTS

In addition to the samples from subjects who had received cetuximab therapy, we analyzed samples from three distinct locations in the United States to investigate the geographic differences in rates of hypersensitivity reaction (Table 1). In group 1, serum samples were available from 76 subjects with cancer who had received cetuximab and whose clinical response had been documented. The case reports were retrospectively evaluated in a blinded manner at Vanderbilt University Medical Center (VUMC), in Nashville. We used a prespecified case definition to determine the presence or absence of a hypersensitivity reaction within 2 hours after the administration of cetuximab and, if present, to score the severity of the reaction. The serum samples that we evaluated included 35 pretreatment samples from VUMC. These samples were obtained from all subjects who had been treated at VUMC for colorectal cancer or cancer of the head and neck between June 2005 and December 2006; of these subjects, 10 had a hypersensitivity reaction that met our case definition.

Group 1 also included 41 samples from subjects at the other centers, including subjects with a history of an adverse event after cetuximab treatment and a nonrandom selection of subjects with no such report. Fourteen of the subjects with an adverse event did not meet our case definition of a hypersensitivity reaction and were categorized as having had no hypersensitivity reaction. The serum samples included those from five subjects at Duke University Medical Center, in Durham, North Carolina (three of whom had a hypersensitivity reaction), and from nine subjects at the Allergy and Asthma Clinic of Northwest Arkansas, in Bentonville, Arkansas (four of whom had a hypersensitivity reaction). Medical reports and serum samples from 27 subjects (8 of whom had a hypersensitivity reaction) were collected from Bristol-Myers Squibb clinical trials at multiple sites.

Groups 2, 3, and 4 were the source of the control serum samples. Group 2 consisted of 72 healthy volunteers at a yearly cancer-screening event held at VUMC, who were matched with subjects with cancer at VUMC for age, sex, race or ethnic group, and smoking status. Group 3 consisted of 49 subjects with cancer of the head and neck (3 of whom had received cetuximab)

who had presented at the Stanford University Medical Center, in Stanford, California. Group 4 consisted of 341 female control subjects who were mothers of children in a large cohort study in Boston.¹⁵ Cohorts 3 and 4 were included as representative samples from areas in which there had been a low prevalence (<1%) of hypersensitivity reactions during cetuximab treatment. The screening of 21 subjects with recurrent anaphylaxis who had presented at the University of Virginia Allergy Clinic identified 11 subjects with positive results on testing for IgE antibodies against cetuximab; serum from 6 of these subjects was used to develop the assays and evaluate specificity.

Representatives of Bristol-Myers Squibb and ImClone Systems reviewed the manuscript, which was written by Drs. Chung, Mirakhur, and Platts-Mills. The study was approved by the institutional review board at each center. Each subject provided written informed consent.

CASE DEFINITION AND GRADING SYSTEM

Our case definition and grading of hypersensitivity reactions were based on documented symptoms listed in the National Cancer Institute Common Toxicity Criteria, version 3.^{11,16} The characteristics of a grade 1 reaction were transient flushing or rash with a fever of less than 38°C (100.4°F); those of a grade 2 reaction were rash or flushing, urticaria, and dyspnea with or without a fever of more than 38°C; and those of a grade 3 reaction were rash, dyspnea, and hypotension. A grade 4 reaction was anaphylaxis. Among 25 subjects who were judged to have had a hypersensitivity reaction, investigators identified 13 mild reactions (grade 1 or 2) and 12 severe reactions (grade 3 or 4) (Table 1). All treatment decisions were made by the local physicians before the serum samples were assayed for IgE antibodies.

EVALUATION OF ANTIGENS

Cetuximab, which is produced by expressing clone C225 in the mouse myeloma cell line SP2/0, was provided by ImClone Systems.^{8,17} A variant of cetuximab, CHO-C225, which is produced in Chinese hamster ovary (CHO) cell lines, was also obtained from ImClone. CHO cells do not produce α -1,3-galactosyltransferase and, for this reason, have a pattern of glycosylation that differs from that of cetuximab.^{17,18} This monoclonal antibody, which was purified by means of the techniques used for cetuximab, had the same affinity for EGFR as did cetuximab. The F(ab')₂ and Fc fragments of cetuximab were prepared by digestion with pepsin and papain, respectively, followed by purification over a protein A column. The molecular weights of these molecules were confirmed by sodium dodecyl sulfate–polyacrylamide-gel electrophoresis. Antigens were biotinylated with the use of sulfosuccinimidyl 6-(biotinamido) hexanoate (EZ-Link, Pierce Biotechnology).¹⁴

Rituximab (Genentech), an anti-CD20 monoclonal antibody, and infliximab (Centocor), a monoclonal antibody against tumor necrosis factor α , were obtained commercially. The reagent galactose- α -1,3-galactose- β ; -1,4-*N*-acetylglucosamine- β ; -spacer-biotin was purchased from Glyco-Tech. Mouse IgG was obtained from Immunology Consultants. Fel d 1, a cat allergen, was purified by affinity chromatography with the use of the monoclonal antibody clone 6F9.¹⁹

IMMUNOCAP IgE ASSAYS

ImmunoCAP is a variation of the radioallergosorbent test in which IgE antibodies that have bound to antigen on the solid phase are detected with a secondary enzyme-labeled anti-IgE antibody.^{14,20} Total and specific IgE antibodies were measured with the use of either ImmunoCAP (Phadia U.S.) or the modified assay with streptavidin-coated ImmunoCAP.¹⁴ All assays on serum samples from subjects who had received cetuximab were performed at the University of Virginia and analyzed in a fashion that was blinded to the scoring of subjects' hypersensitivity reactions. Cetuximab was biotinylated, and approximately 5 μ g was added to

each streptavidin-coated ImmunoCAP before serum was added. The assays were performed with the ImmunoCAP250 instrument, and the results were expressed as international units (IU) per milliliter (with 1 IU equivalent to approximately 2.4 ng). The threshold value for a positive reaction was 0.35 IU per milliliter. The streptavidin Immuno-CAP technique was also used to measure IgE antibodies against CHO-C225, the F(ab')₂ and Fc fragments, galactose- α -1,3-galactose, mouse IgG, rituximab, infliximab, and Fel d 1. ImmunoCAP assays were used to test selected serum samples for IgE antibodies against allergens from dust mites, cats, dogs, German cockroaches, grass pollen, ragweed pollen, beef, pork, and cow's milk.

STATISTICAL ANALYSIS

The limiting factor in our study was the number of serum samples available from subjects who had a hypersensitivity reaction. Using consistent grading criteria, we identified 25 such subjects, who were matched with sequential controls (for subjects from Tennessee) or with nonrandom controls (for subjects from other states). We compared the results for IgE antibodies in these 25 subjects with results in 51 subjects who did not have a hypersensitivity reaction, using chi-square analysis, and expressed the results as the natural logarithm of the odds ratio. We compared quantitative measures of IgE antibodies against cetuximab and IgE antibodies against galactose- α -1,3-galactose and cat, beef, grass, pollen, and dust-mite allergens with the use of Spearman's rank-order correlation. Statistical analyses were performed with SPSS software, version 13.0 (SPSS). A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

SERUM ASSAYS FOR IgE ANTIBODIES

Serum samples that were positive for IgE antibodies against cetuximab had antibody titers ranging from 0.38 to 140.00 IU per milliliter. Table 2 shows results for 6 subjects who had anaphylaxis after receiving cetuximab, 11 subjects who had no reaction to cetuximab, and 6 who had recurrent anaphylaxis or angioedema unrelated to cetuximab treatment. Evidence that the assay detected IgE antibodies against cetuximab included the detection of these antibodies by the monoclonal anti-IgE antibody used with the ImmunoCAP assay, demonstration that more than 95% of the IgE antibodies bound to the F(ab')₂ portion of cetuximab, and the finding that absorption of the serum with the use of a monoclonal anti-IgE antibody depleted binding to cetuximab and total levels of IgE in parallel (Table 2).

PREEXISTING IgE ANTIBODIES

Of a total of 538 serum samples from the four groups, 38 contained IgE antibodies against cetuximab (Fig. 1). Among the 76 selected subjects who had received cetuximab, 25 had a hypersensitivity reaction; of these subjects, 17 had a positive test for IgE antibodies against cetuximab in pretreatment serum, whereas only 1 of 51 subjects who did not have a hypersensitivity reaction had such antibodies before treatment with cetuximab (\log_e of the odds ratio, 4.7; $P < 0.001$). The sensitivity and specificity of a positive assay for IgE antibodies for any hypersensitivity reaction were 68% and 98%, respectively. For severe hypersensitivity reaction, these values were 92% and 90%, respectively. Subjects with IgE antibodies against cetuximab had a higher rate of severe hypersensitivity reaction than did subjects without such antibodies ($P = 0.03$ by Fisher's exact test). Among the eight subjects who were reported to have had a hypersensitivity reaction but had negative results on the IgE assay, seven had grade 1 or 2 reactions, and only one subject had a grade 3 reaction. Five of the eight subjects were rechallenged; of these subjects, one had a second hypersensitivity reaction, and four completed treatment without further reactions. Of the subjects who were subsequently found to have IgE antibodies against cetuximab, 17 had discontinued therapy.

Among control subjects in Tennessee, 15 of 72 serum samples (20.8%) had positive results on testing for IgE antibodies against cetuximab. In these samples, both the prevalence and titers of IgE antibodies against cetuximab were similar to those in samples from the treated subjects (Fig. 1). Among subjects with cancer of the head and neck in California and female control subjects in Boston, 3 of 49 serum samples (6.1%) and 2 of 341 (0.6%), respectively, had IgE antibodies against cetuximab (Fig. 1). These low rates in cohorts 3 and 4 parallel the low rates of hypersensitivity reactions that were reported with cetuximab treatment in those regions.¹¹

CHARACTERIZATION OF THE EPITOPE ON CETUXIMAB

Given that the IgE antibodies were specific for the Fab portion of the heavy chain of cetuximab, the relevant epitope could be a mouse amino acid sequence or an oligosaccharide on this segment of the molecule (Fig. 2). The absence of binding to other chimeric monoclonal antibodies (e.g., rituximab and infliximab) and the absence of IgE antibodies against cetuximab in 25 samples from allergic subjects who had IgE antibodies against mouse proteins²¹ argue against the role of a mouse amino acid sequence (Table 3). The Fab portion of the cetuximab heavy chain is glycosylated at N88 with a range of sugars, including galactose- α -1,3-galactose and a sialic acid, *N*-glycolylneuraminic acid (NGNA).¹⁷ To test whether the IgE antibodies were specific for the oligosaccharides, samples containing IgE antibodies against cetuximab were assayed for IgE antibodies that could bind to CHO-C225. These assays were negative for 11 cetuximab-treated subjects and for 5 of the 6 subjects who had an anaphylactic reaction after receiving cetuximab (Table 3). In addition, in 150 samples from groups 1 and 2, as well as those listed in Table 3, assays for IgE antibodies against galactose- α -1,3-galactose correlated with results for antibodies that bound to cetuximab ($r = 0.92$, $P < 0.001$). Most of the positive samples also contained IgE antibodies against cat, dog, and beef proteins but not against mite allergens or pollens (Table 3, and Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

The correlation with IgE antibodies against mammalian proteins is consistent with the presence of galactose- α -1,3-galactose on proteins of most nonprimate mammals. To confirm the specificity of the reaction, we showed that the binding of IgE antibodies against cat, dog, beef, and pork proteins and cetuximab was inhibited by soluble galactose- α -1,3-galactose and could be absorbed out of the serum with porcine thyroglobulin, which is glycosylated with galactose- α -1,3-galactose (Table 2 of the Supplementary Appendix).

DISCUSSION

Severe anaphylactic reactions have been reported after treatment with several different monoclonal antibodies, but the mechanism of these reactions has not been defined, and their rates have generally been less than 1%.^{1-5,7,8,22} Our results show that most of the severe hypersensitivity reactions to cetuximab in the subjects we studied were associated with IgE antibodies against galactose- α -1,3-galactose that were present before treatment with cetuximab. The assay we used identified 17 of the 21 subjects whose treatment had to be discontinued after the first infusion because of a hypersensitivity reaction.

Unlike most other monoclonal antibodies, cetuximab is produced in the mouse cell line SP2/0, which expresses the gene for α -1,3-galactosyltransferase.^{17,18} The evidence that IgE antibodies that are specific for the post-translational modification of a molecule can cause severe infusion reactions may have relevance for an understanding of allergic responses to other recombinant molecules.

It is now recognized that all humans have IgG antibodies specific for the oligosaccharide galactose- α -1,3-galactose, which is closely related to substances in the ABO blood group.²³⁻²⁵ This oligosaccharide is one of the major barriers to the transplantation of organs from

other mammals in humans and has prompted the development of a strain of pigs in which the gene for α -1,3-galactosyltransferase has been knocked out.^{24,26}

Natural exposure to galactose- α -1,3-galactose appears to induce the production of IgE antibodies against galactose- α -1,3-galactose in some people. The presence of such IgE antibodies before treatment may put patients who receive monoclonal antibodies containing galactose- α -1,3-galactose at risk for hypersensitivity reactions. The rapid reactions to cetuximab may be explained by intravenous injection, and the presence of galactose- α -1,3-galactose on both Fab segments of the cetuximab antibody allows for the efficient cross-linking of IgE on mast cells (Fig. 2). Patients who have such antibodies do not report a rapid onset of allergic symptoms after the ingestion of beef, pork, or cow's milk. However, we have identified a series of patients with IgE antibodies against galactose- α -1,3-galactose who reported having had episodes of anaphylaxis or severe angioedema 1 to 3 hours after eating beef or pork (unpublished data). The explanation for such a delayed reaction is not clear, but a similar delay has been reported in patients with IgE antibodies against carbohydrate epitopes of plant proteins.^{27,28} In addition, it has recently been reported that some patients with cat allergy have IgE antibodies that bind to a carbohydrate epitope on cat IgA.²⁹

The high prevalence of hypersensitivity reactions to cetuximab in the Southeast is supported by our own data from the Tennessee group and in other recent studies.¹¹ The striking difference in the prevalence of the IgE antibodies against cetuximab provides an explanation for the difference in rates of clinical hypersensitivity reaction between subjects in Boston or northern California and those in Tennessee, Arkansas, or North Carolina.^{6,11,30} A high prevalence of IgE antibodies against neuromuscular blocking agents in Norway was found to be associated with anaphylaxis, and the difference in incidence between Norway and Sweden was attributed to suxamethonium, an ingredient in a commonly used cough syrup in Norway.^{31,32} The explanation for the regional distribution of IgE antibodies against galactose- α -1,3-galactose in the United States is not clear. Most humans have IgG antibodies against galactose- α -1,3-galactose,²⁴⁻²⁶ but we do not know why people in one area of the country have IgE antibodies against galactose- α -1,3-galactose, whereas in other areas the incidence of such IgE antibodies is very low. The regional exposures that could be relevant include histoplasmosis, ameba, tick bites, coccidioidomycosis, nematodes, or cestodes. The effect does not appear to be a nonspecific enhancement of IgE production, since we found little or no association with IgE antibodies against allergens other than those derived from mammals.

In conclusion, we have identified a mechanism underlying a hypersensitivity reaction to cetuximab, preexisting IgE antibodies against an oligosaccharide present on the recombinant molecule. Our results have implications for evaluating risks associated with antibody-based therapeutics and for understanding the relevance of IgE antibodies specific for post-translational modifications of natural and recombinant molecules.

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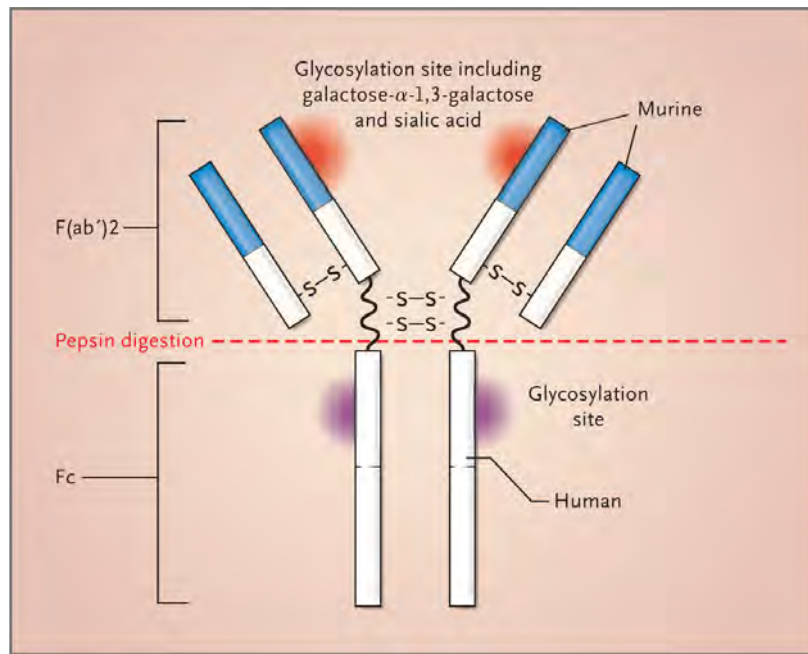


Figure 2. Structure of Cetuximab

The amino acid sequence of cetuximab has potential glycosylation sites at Asn43 of the light chain and at Asn88 and Asn299 of the heavy chain. The sugars on the Fab portion include galactose- α -1,3-galactose and the sialic acid *N*-glycolylneuraminic acid. In contrast, the glycosylation site at Asn43 is not glycosylated, and glycosylation of the Fc portion of the heavy chain includes only oligosaccharides that are commonly present on human proteins.^{17,18} S-S denotes a disulfide bond.

Table 1

Characteristics of the Study Groups.*

Variable	Tennessee Case Subjects (N = 35)	Group 1 Other Case Subjects (N = 41)	Group 2 Tennessee Control Subjects (N = 72)	Group 3 California Control Subjects (N = 49)	Group 4 Boston Control Subjects (N = 341)	Total All Groups (N = 538)
Age (yr)						
Median	58	63	58	58	NA	58
Range	43–93	41–81	32–82	36–97		32–97
Sex						
Male:female ratio	22:13	22:19	40:32	37:12	0:341	121:417
Male (%)	63	54	56	76	0	22
Race or ethnic group (no.) [†]						
White	33	35	65	23	236	392
Black	2	5	7	2	54	70
Other	0	1	0	2	32	35
Unknown	0	0	0	22	19	41
Tobacco use (no.)						
Total						197
Current	18	14	16	0	NA	48
Former	3	11	25	0	NA	39
Never	13	16	31	0	NA	60
Unknown	1	0	0	49	341	391
Tumor site (no.)						
Total						125
Head and neck	18	5	16	49	NA	72
Colorectal	17	35	25	0	NA	52
Lung	0	1	0	0	NA	1
Clinical stage (no.)						
Total						76
I or II	9	4	NA	NA	NA	13
III	8	6				14
IV	14	25				39
Unknown	4	6	NA	NA	NA	10
Hypersensitivity reaction (no.)						
Total						26
Rated by investigators						
Low-grade	6	7				13
High-grade	4	8				12
Late response	1	0				1
Rated retrospectively [‡]						
Low-grade	0	2				2
High-grade	11	13				24

* NA denotes not available.

[†] Race or ethnic group was reported by the subjects.

[‡] Retrospective scoring of the severity of hypersensitivity reactions was performed by blinded analysis of case reports.

Table 2

IgE Antibodies against Cetuximab and the Fragments of the Molecule for 12 Subjects Who Had a Severe Hypersensitivity Reaction.*

Type of Reaction and Subject No.	Total IgE	Cetuximab [†]	Fragment of Cetuximab Molecule [†]	Rituximab [†]	Depletion with Total IgE Remaining	IgE Antibodies Remaining [‡]	
			F(ab) ₂			percent	
			international units per milliliter				
Hypersensitivity reaction							
Anaphylaxis related to cetuximab							
1 [§]	3161.0	41.6	40.9	0.35	1.3	1.0	
2	887.0	38.8	52.3	ND	8.9	12.0	
3 [§]	374.0	20.2	26.0	0.35	3.4	3.2	
4 [§]	348.0	11.1	13.2	0.35	9.1	5.2	
5	58.5	4.9	5.7	0.35	29.0	21.0	
6 [§]	22.2	4.2	6.6	0.35	15.0	8.4	
Recurrent anaphylaxis unrelated to cetuximab[†]							
7	1081.0	131.0	158.0	2.90	4.9	4.0	
8	243.0	69.2	86.8	1.20	0.9	4.0	
9	242.0	55.1	99.6	0.35	9.6	6.7	
10	188.0	43.5	45.8	0.35	11.1	5.9	
11	538.0	81.1	100.0	0.35	1.4	5.7	
12	63.6	13.0	17.9	0.57	11.0	4.9	
Mean	315.0 ^{//}	26.7	33.4	1.26 ^{**}	5.7	5.3	
No hypersensitivity reaction	17.4 ^{††}	0	0	0	NA	NA	

* NA denotes not applicable, and ND not determined.

[†]The assay was performed with biotinylated antigen on streptavidin ImmunoCAP.

[‡]Onalizumab (monoclonal anti-IgE antibody) that was bound to protein A agarose beads was incubated overnight at 4°C at a 1:5 bead-to-serum volume ratio.

[§]The subject had grade 4 anaphylaxis.

^{//}Subjects presented to the University of Virginia Allergic Disease Clinic with recurrent angioedema or anaphylaxis and had a positive test for IgE cetuximab-binding antibodies. Subjects 7 through 10 had severe episodes of anaphylaxis, and Subjects 11 and 12 had severe episodes of angioedema.

^{††}The IgE value is the geometric mean for 12 cetuximab-treated subjects who had a hypersensitivity reaction (95% CI, 130.0 to 760.0).

**The mean is for results from 3 of 10 subjects.

^{‡‡}The IgE value is the geometric mean for 11 cetuximab-treated subjects who did not have a hypersensitivity reaction (95% CI, 6.8 to 45.0).

Table 3

Specificity of the IgE Antibodies That Cross-React with Cetuximab.*
 Type of Reaction and Subject No.

Type of Reaction and Subject No.	Type of Cetuximab [†] SP2/0 [‡]	CHO [‡]	Galactose- α -1,3-Galactose ^{§§} international units per milliliter				
			Cat	Dog	Fel d 1 [‡]	Beef	Mouse IgG [‡]
Hypersensitivity reaction							
Anaphylaxis related to cetuximab							
1	41.6	0.35	3.16	2.60	0.35	3.02	
2	38.8	0.35	13.20	12.30	0.35	12.46	
3	20.2	0.35	9.34	9.77	0.35	6.92	
4	11.1	0.35	1.94	1.86	0.35	1.82	
5	4.9	0.35	0.35	0.35	0.35	0.35	
6	4.2	0.35	1.54	1.50	0.35	1.66	
Recurrent anaphylaxis unrelated to cetuximab [¶]							
7	131.0	1.89	41.50	34.50	3.64	32.90	
8	69.2	0.35	27.70	32.00	0.35	26.20	
9	55.1	0.35	22.20	25.10	0.35	13.80	
10	43.5	0.35	37.30	29.40	0.35	3.48	
11	81.1	0.35	14.30	14.70	0.35	8.75	
12	13.0	0.35	8.86	8.84	0.35	8.90	
Mean	27.7	NA	10.30	9.93	NA	7.16	
No hypersensitivity reaction	0	0	0	0	0	0	

*NA denotes not applicable, and ND not determined.

[†]Cetuximab is produced by expressing clone C225 in the mouse myeloma cell line SP2/0. A variant of cetuximab is produced in Chinese hamster ovary (CHO) cell lines. Since CHO cells do not produce α -1,3-galactosyltransferase, they have a pattern of glycosylation that differs from that of SP2/0.

[‡]The assay was performed with biotinylated antigen on streptavidin ImmunoCAP.

[§]The assay was performed with galactose- α -1,3-galactose- β -1,4-*N*-acetylglucosamine- β -spacer-biotin, which binds to streptavidin ImmunoCAP.

[¶]Subjects presented to the University of Virginia Allergic Disease clinic with recurrent angioedema or anaphylaxis and had a positive test for IgE antibodies against cetuximab. Subjects 7 through 10 had severe episodes of anaphylaxis, and Subjects 11 and 12 had severe episodes of angioedema.

^{||}For statistical analysis of the positive and negative relationships with other allergens, additional data are available in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

ANALYSIS

Suitability of common drugs for patients who avoid animal products

Many patients avoid eating animal products for various reasons, but how many doctors consider this when prescribing a drug? Even if they do, **Kate Tatham** and **Kinesh Patel** find it is hard to determine whether drugs meet the patient's dietary requirements

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Specific dietary preferences regarding animal products in food are common in the general population.¹ Influences such as religion, culture, economic status, environmental concern, food intolerances, and personal preferences all play a part in the foods that people choose to consume. In the United Kingdom, Food Standards Agency data indicate that 5% of population are vegan or vegetarian, increasing to 12% in non-white people.² Vegetarians are defined as individuals that do not consume foods either directly obtained or using products from the slaughter of an animal, whereas vegans do not consume any foods originating from animals.^{3,4} Some religious groups also avoid certain animal products.

Many patients and doctors are unaware that commonly prescribed drugs contain animal products—for example, low molecular weight heparin (pigs), Gelofusine (cows), and conjugated oestrogen (Premarin, horses). Furthermore, with some commonly used ingredients, simply reading the list of ingredients will not make it clear whether the product meets the patient's dietary preferences.

Problem ingredients

Lactose, which is derived from cows' milk, is traditionally extracted using bovine rennet. It is used as a filler and diluent powder and as an aid in the manufacturing of medications. Some manufacturers now use vegetarian processes to extract lactose from milk, leading to potential confusion about its suitability for vegetarians.

Similarly, gelatine is widely used to encapsulate medications and is sourced from bovine or porcine skin, hide, or bone and occasionally fish. If derived from pigs it can be a problem for some Muslims and Jews. The largest kosher certification body, the Orthodox Union's Kosher division, does not accept porcine gelatine as kosher⁵ whereas other Jewish organisations are more permissive. In 1995, the World Health Organization held a seminar for religious scholars to discuss the consumption of porcine products in medications by Muslims. This concluded

that the gelatine formed from the transformation of impure bones was itself pure and the ingestion of such products was permitted.⁶ Despite these reassurances, last year a campaign to vaccinate children in Scotland against influenza was halted because of concern in the Muslim community about pork gelatine within the vaccine.⁷ Other published data have shown similar levels of concern among certain ethnic groups regarding gelatine ingestion.¹ These concerns have even prompted Saudi Arabia and Malaysia to collaborate to produce camel gelatine in an effort to meet the rising demand for non-porcine products.

Another common ingredient is magnesium stearate, a lubricant used in tablet processing and improves the solubility of medications. Historically it was sourced from the rendered fat of cows, pigs, and sheep, but now it can also be produced from vegetable matter.

How common are animal derived products?

Even though the absolute levels of animal products in many medications are likely to be minimal, adherence to religious doctrine can be dogmatic, and doctors need to consider this when prescribing. To ascertain the scale of the problem, we investigated the frequency with which animal products are found in the commonly prescribed medications in primary care in the United Kingdom by searching various public sources (box)

We identified the 100 most commonly prescribed drugs in primary care in January 2013 from the NHS Business Services Authority. Of these, 74 contained one or more of lactose, gelatine, or magnesium stearate (table 1⇓). Lactose was found in 59 medications, of which 48 had accompanying public assessment reports—the only information source referring to the origins of excipients. In 10 cases (21%), the report did not specifically declare that the medication contained material of animal origin. Of the 38 reports mentioning animal content, the

Sources of information on content of drugs

British National Formulary (BNF)
 UK Medicines and Health Products Regulatory Agency public assessment reports
 Summary of product characteristics
 European Medicines Agency public assessment reports
 Patient information leaflets
 Drug packaging

method used for the production of lactose was stated only in a minority of cases, with eight (21%) declaring the use of calf rennet. When the use of animal rennet was not declared, we contacted the manufacturers of the 10 most commonly prescribed medications in this category. Of 10 manufacturers contacted, five responded. One manufacturer confirmed that the lactose was rennet-free with four confirming the use of calf rennet.

Magnesium stearate was found in 49 of the top 100 medications, with the animal form declared in four products and the vegetarian form confirmed in 31. Fourteen products had no information on provenance.

Gelatine was used in 20 drugs. However, two of the product assessment reports wrongly stated that there was no animal content and seven did not mention animal content. Of the 11 that stated the presence of ingredients of animal origin, eight did not identify the animal used, one listed porcine origin, one bovine origin, and one both porcine and bovine origin.

Accessing the information

We found that it was difficult to determine the suitability of common drugs for patients with specific dietary preferences. Furthermore, suitability varied between different formulations of the same product (table 2). Although the presence of lactose was declared on 90% of exterior packaging, this was the case for only 19% of medications containing gelatine, and the presence or absence of animal derived products was never disclosed. The *British National Formulary* provides only medication indications, contraindications, dosage, and cost. Patient information leaflets and summaries of product characteristics listed the excipients but did not specify the origins. Only the Medicines and Health Products Regulatory Agency product assessment report provided statements regarding animal product contents, but even these were inconsistent, incomplete, and on two occasions wrong. In all the data sources analysed, there was no statement about the suitability of gelatine containing preparations for vegetarians.

Differentiation between vegetarian and non-vegetarian lactose was poor, with the manufacturing processes and materials involved not usually divulged. Contact with manufacturers of lactose containing products also revealed uncertainty about whether medications were suitable for vegetarians. One manufacturer stated: "though calf rennet is used to extract lactose from milk, however it does not appear on the tablet and hence tablets are suitable for vegetarians," although this definition of vegetarianism would not be consistent with that of either the Food Standards Agency or the Vegetarian Society.

Our data suggest that it is likely that patients are unwittingly ingesting medications containing animal products with neither prescriber nor dispenser aware. Previous studies assessing the acceptability of oral gelatine containing medication to patients found that 40% of patients in an inner city area would prefer to take medication without animal derived products.¹

Though national, international, and religion specific recommendations may exist, individual patient choice should be paramount and it is difficult to predict preferences. It therefore seems prudent for prescribers to ask patients about their preferences to avoid non-adherence, which is a major healthcare concern. Up to half of prescribed medications are not taken as directed, and the National Institute for Health and Care Excellence has recommended that healthcare professionals ask about and address patients' specific concerns before prescribing.⁸ For prescription medications in taxpayer funded healthcare systems, such as in the United Kingdom, patients have little choice about the exact pharmaceutical preparation dispensed by their pharmacist. There have been reports of medications being discontinued without medical consultation to avoid the ingestion of animal derived products with documented adverse effects on patients.⁹ Poor labelling also hinders the ability of patients to find over the counter medicines that conform to their requirements.

Better labelling

Information about animal derived products in medicines is difficult to obtain, unclear, inconsistently reported, and sometimes incorrect. Improvement in drug labelling, mirroring those standards advised for food where manufacturers voluntarily use the Vegetarian Society's seedling symbol, would help inform prescribers, dispensers, and patients. However, manufacturers in the EU are currently prohibited from making statements in product information leaflets about suitability for vegetarians or vegans as these are deemed to be "lifestyle choices." A change to this rule to permit a simple statement about animal content in medications would be easy to implement and improve clarity and patient choice.

Current legislation in Europe mandates listing all the contents of medications in often lengthy patient information leaflets accompanying products. But the origin of the contents is not specified and the introduction of such a requirement would undoubtedly allay many concerns.

Labelling on exterior packaging would be an even more accessible way of communicating with patients and pharmacists. European guidelines on the listing of ingredients on exterior packaging do exist but include only those substances that may cause a medical adverse reaction, such as sucrose in patients with sucrase-isomaltase insufficiency. No standards have been proposed for those with dietary preferences.

It is unlikely that any labelling standard could address all dietary requirements, and the ultimate solution would be to eliminate animal derived products where possible from medications. The first vegetarian capsules, made from hypromellose, were produced in 1989 and production has expanded significantly since then as demand for gelatine-free medications has grown.¹⁰ Other than the benefits to patients with dietary preferences, use of these capsules avoids the need for compliance with regulations regarding bovine spongiform encephalopathy.

Lactose is already produced by some manufacturers without using rennet; magnesium stearate can be made chemically without animal ingredients. Although vegetarian friendly ingredients may be more expensive than those produced by traditional processes, the costs would diminish as production expanded and they would limit the exposure of patients to products they find unacceptable.

Contributors and sources: KT is a clinical research fellow in anaesthetics and intensive care with a long term interest in delivering effective patient care. KP is a research fellow in gastroenterology working in an area with a large ethnic minority population. The article arose from observations and discussions around the blanket administration of medications such as intravenous Gelofusine to various ethnic groups while simultaneously offering hospital food options to suit restricted dietary preferences. KT had the idea for the article and collected the data. KT and KP jointly interpreted the data, drafted the manuscript, and approved the final version. KT is guarantor.

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Key messages

Most medications prescribed in primary care contain animal derived products and it is unclear whether they are suitable for vegetarians
 Labelling of animal content in medication is poor and variably instituted
 Patients with specific dietary restrictions are likely to be consuming animal products unwittingly
 Disclosure of animal content and excipients would help patients make an informed personal choice

Statement from the MHRA

This issue has been considered in previous reviews of labelling policy and has been discussed within a number of European forums. There is no opportunity for the UK to act unilaterally in the area of medicines labelling so we cannot take our own action. On the issue of "suitable for vegetarians/vegans" under the regulations, although some ingredients are derived from animals, many of these are now also derived from plant sources. There is no requirement for a company to declare how an inactive ingredient is sourced at the time of licensing. Only information which is supported by the licence documents can be referenced in the labelling of a medicine.

Tables**Table 1 | Identification of animal derived products in 100 most common drugs in primary care**

	No of drugs	No not suitable for vegetarians	No suitable for vegetarians	Unknown
Lactose	59	12*	1	46
Gelatine	20	20†	0	0
Magnesium stearate	49	4	31	14

*Calf rennet used in production.

†Two stated that gelatine was porcine derived and one that it was bovine; the remainder gave no information on animal source.

Table 2 | Information available on animal content of 10 most commonly prescribed drugs from MHRA public assessment reports or summary of product characteristics

Drug/ manufacturer	Suitable for vegetarians	Gelatine		Lactose		Magnesium stearate		Information in MHRA report
		Present	Which animal identified	Present	Calf rennet used?	Present	Animal derived	
Simvastatin								
Tillomed	No	No	—	Yes	Not stated	Yes	Not stated	None
M & A Pharmachem								None of excipients excluding MS contain material of animal origin. "Milk used in the production of lactose ... is sourced from healthy animals"
	No	No	—	Yes	Not stated	Yes	Yes	
Kent Pharmaceuticals	Unknown	No	—	Yes	Not stated	Yes	Not stated	None
Aspirin								
Bristol Laboratories								"No other materials [excluding lactose] ... of animal origin are included in the product"
	Yes	No	—	Yes	Not stated	No	—	
Intrapharm Laboratories	Yes	No	—	Yes		No	—	Not available
Actavis	Unknown	No	—	No	—	Yes	Not stated*	Not available
Paracetamol								
Rockspring Healthcare	Yes	No	—	No	—	Yes	No	"None of the excipients contain materials of animal ... origin"
Medreich	Yes	No	—	No	—	Yes	No	"None of the products contain material of animal ... origin"
Peter Black	Yes	Yes	No	No	—	Yes	No	"Magnesium stearate is not derived from animal origins"
Levothyroxine								
Amdipharm	Yes	No	—	Yes	Not stated*	Yes	Not stated*	Not available
Actavis	Unknown	No	—	Yes	Not stated*	Yes	Not stated*	Not available
Wockhardt	Unknown	No	—	Yes	Not stated*	Yes	Not stated*	Not available
Omeprazole								
Zanza			No (states no animal products)					"No material of ... animal origin contained or used in the manufacturing process"
	No	Yes		No	—	No	—	
Winthrop								Lactose and gelatin ... are materials of animal origin ... lactose is prepared without the use of ruminant material other than milk and calf rennet"
	No	Yes	No	Yes	Yes	No	—	
Teva								"With the exception of gelatin, none of the excipients contain materials of animal ... origin"
	No	Yes	No	No	—	No	—	
Lansoprazole								
Jenson			No (states no animal products)					"There are no materials of ... animal origin contained in or used in the manufacturing process for this product"
	No	Yes		No	—	No	—	
Teva	Unknown	No	—	Yes	Not stated	Yes	Not stated	None
Dexcel								"With the exception of gelatin, none of the excipients contain materials of animal ... origin"
	No	Yes	No	No	—	No	—	
Salbutamol								
STD Pharmaceuticals	Yes	No	—	No	—	No	—	"None of the excipients contain materials of animal ... origin"
Noeolab	Yes	No	—	No	—	No	—	None
Ramipril								
Pliva	No	Yes	Yes	No	—	No	—	"Gelatin of bovine and porcine origin may be used"

Table 2 (continued)

Drug/ manufacturer	Suitable for vegetarians	Gelatine		Lactose		Magnesium stearate		Information in MHRA report
		Present	Which animal identified	Present	Calf rennet used?	Present	Animal derived	
Aurobindo	No	Yes	—	No	—	No	—	"The only excipient that contains material of animal ... origin is gelatine"
Teva	Yes	No	—	No	—	No	—	None
Amlodipine								
Arrow	Yes	No	—	No	—	Yes	Not stated	None
Ivoven	Yes	No	—	No	—	Yes	No	"None of the excipients are sourced from animal ... origin"
Quality	Yes	No	—	No	—	Yes	No	"Magnesium stearate ... is of vegetable origin ... no materials of animal origin are used in the manufacture of the tablets"
Atorvastatin								
Dexcel	No	No	—	Yes	Not stated	Yes	Not stated	None
Teva	Yes	No	—	No	—	Yes	No	"None of the excipients are of animal ... origin"
Alkaloid	Unknown	No	—	Yes	Not stated	Yes	No	"With the exception of lactose ... none of the excipients contain materials of animal ... origin"

*No public assessment report available and information not included in summary product of characteristics.

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Glycerin (Glycerol)

What is glycerin?

Glycerin is chemically a [sugar alcohol](#) ^[1]. On the Nutrition Facts labels, it is included in total [carbohydrates](#), and, as a subcategory, in sugar alcohols ^[2]. In the EU, glycerin is listed as E number **E422**.

Glycerin Word Origin and Meaning

From French *glycérine*, from Greek *glukeros* = sweet ^[13].

Nutrition Facts:

- Calories per gram = 4.3
- Glycemic index (GI) = ?
- Sweetness, relative to [sucrose](#) = 75%
- Net carbs = probably 100%

Glycerin, Glycerine and Glycerol Are the Same

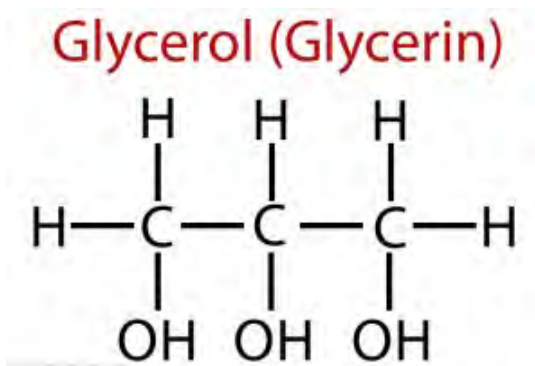
Glycerin, glycerine and glycerol are 3 names for the same substance. The name glycerin or glycerine is usually used as a product name and the name glycerol for the ingredient, for example, glycerin syrup contains 99.7 glycerol.

Glycerol vs triglycerides. Glycerol naturally occurring in foods and in the human body is usually joined with fatty acids and forms triglycerides, which are [lipids](#), but again, glycerol as a standalone molecule is not a lipid but carbohydrate.

When triglycerides are digested, they are broken down into glycerol and fatty acids, which are absorbed.

Formula

The chemical formula of glycerin (glycerol) is $C_3H_5(OH)_3$.



Picture 1. Glycerol structure

Glycerin Absorption and Metabolism

Glycerin is chemically classified as a sugar alcohol, but it is more similar to sugars: it is readily absorbed and is probably converted into [glucose](#) in the human body and it provides 4.3 kilocalories of energy per gram ^[2,3]. Glycerin is not one of the [FODMAPs](#) (fermentable oligo-, di- and monosaccharides and polyols), because it is well absorbed in the small intestine and does not pass to the large intestine where it would be fermented by intestinal bacteria.

Glycerin is often mentioned as a sweetener with a low glycemic index, but there are no reliable sources to confirm this.

Types of Edible Glycerin

Vegetable glycerin is made from vegetable oils (palm oil, palm stearin, palm kernel oil, coconut oil, soybean oil) during production of soap or biodiesel.

Animal glycerin is a natural byproduct of animal [fats](#) (such as beef tallow) during production of soap.

Synthetic glycerin is produced from cane or corn syrup sugar, or propylene (a petroleum derivative).

Glycerin as a Food Additive

Food-grade glycerin may be added as a humectant (wetting agent), thickener, solvent or sweetener to dairy products (cream), canned goods, confections, fondant, processed fruits, jams, energy bars and other foods. The source of glycerin (animal or vegetable oil, corn syrup, petroleum) used in a food product is usually not revealed on the food labels.

Other Glycerin Uses

- An emulsifier in pills, syrups, toothpastes, mouth washes, [fluoride](#) gels, tobacco, etc.
- Anhydrous glycerin is used in fluoride gels, and is approved as an over-the-counter (OTC) anti-caries drug by US Food and Drug Administration (FDA) ^[14].
- A lubricant, enema or laxative, as a suppository is used to treat constipation.
- Oral glycerin, as a drug, is used to lower high pressure within the eye (glaucoma).
- Intravenous glycerin can be used to treat brain swelling (cerebral edema) ^[7].
- Glycerin may be used as a skin or hair moisturizer.

Possible Glycerin Health Benefits

In some studies, glycerin in doses about 30 mL/kg body weight slightly (by 2.6%) increased hyperhydration and endurance performance, but additional research is warranted ^[12].

Glycerin Safety

Glycerin as a food additive is Generally Recognized As Safe (GRAS) US Food and Drug Administration (FDA) ^[6].

Glycerin is expected to be safe to use by adults and ^[7]children . Glycerin has no known cancer-promoting (carcinogenic), DNA-damaging (mutagenic) or birth defect-causing (terato^[4]genic) effects .

During Pregnancy

Glycerin is category C substance, which means side effects were possibly observed in animal fetuses but not in human fetuses due to lack of human studies ^[7].

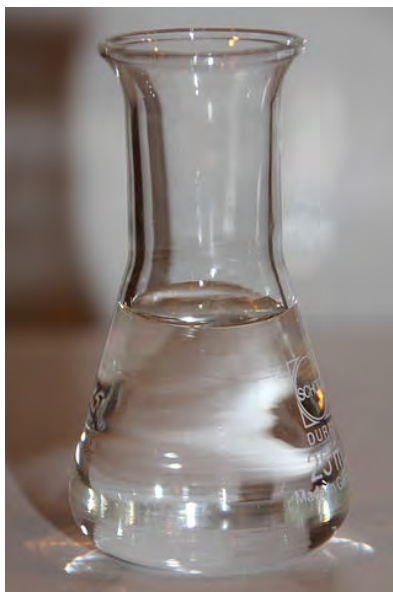
Side Effects, Dangers

Glycerin as a sweetener used in foods does not likely cause any side effects.

Glycerin as a laxative can cause dry mouth, nausea, headache, diarrhea, excessive urination (polyuria) and eventual dehydration ^[7].

In individuals who are sensitive to palm or coconut oil, vegetable glycerin may trigger allergic reactions.

Liquid Glycerin (Syrup) and Cooking



Picture 2. Glycerin is a thick, translucent liquid (source: Wikimedia, Creative Commons licence)

USP-grade* or food-grade glycerin syrup properties:

- A translucent, thick, viscous **syrup**, without odor; contains 99.7% of glycerol ^[8,9]
- 75% as sweet as **sucrose**
- **Highly hygroscopic** - readily attracts moisture ^[11]
- **Soluble** in cold and hot **water** and in **alcohol** ^[4]
- **Melting point** = 64.4°F (18°C) ^[8]
- **Boiling point** = 554 °F (290 °C) ^[8,11]

* USP = US Pharmacopeia

^[2]

Frequently Asked Questions

1. Is glycerin vegan?

- Vegetable glycerin is usually vegan, but yeasts or bacteria may be used during the purification process.
- Synthetic glycerin is vegan.
- Animal **protein** is not vegan.

2. Is glycerin syrup appropriate for diabetics?

Currently, the effect of glycerin on blood glucose levels is not known; it may be similar to the effect of table sugar.

Related Nutrients

- [Sugar alcohols \(polyols\)](#)
- [Sugars](#)
- [Carbohydrates](#)

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