



## How to Treat Quiz

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*Ixodes holocyclus.*

IMAGE COURTESY STEPHEN DOGGETT, NSW HEALTH PATHOLOGY, WESTMEAD, NSW.

### NEED TO KNOW

The most commonly seen tick-bite-induced allergies are mammalian meat allergy (MMA) and tick anaphylaxis.

Tick anaphylaxis, an immediate IgE-mediated condition, is diagnosed clinically and may be fatal.

MMA is emergent worldwide and is classically a delayed (typically by 3-6 hours), 'middle-of-the-night', rapidly evolving, severe anaphylaxis in an individual with a history of tick bite.

Amplifying factors for food allergy reactions are often pivotal in eliciting symptoms in MMA.

Detection of galactose-alpha-1,3-galactose-specific (alpha-gal-specific) IgE is useful in confirming a diagnosis of mammalian meat allergy after tick bite, stratifying the risk of a reaction and serving as a baseline in long-term management.

Consequences of developing alpha-gal-specific IgE are multiple and mostly therapeutic – for example, vaccines, heparin, cetuximab – but evidence suggests other non-communicable, non-allergic diseases may arise from alpha-gal sensitisation via tick bites.

Primary and secondary prevention of all tick-induced allergies depends on implementation of Australian-developed, evidence-based tick-bite prevention and management strategies.

Refer all patients with suspected or proven tick-induced allergies for specialist opinion if in any doubt as to the diagnosis, interpretation of investigations, implications or long-term management.

# Tick-induced mammalian meat allergy and tick anaphylaxis



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## BACKGROUND

TICK-induced allergies – chiefly, mammalian meat allergy after tick bite and tick anaphylaxis – have become increasingly prevalent in Australia this century.<sup>1,2</sup> Tick-induced allergies predominantly occur on the eastern seaboard.<sup>2</sup> Tick anaphylaxis is most prevalent in Australia.<sup>2</sup> Mammalian meat allergy (MMA) after tick bite has now been reported on all six continents where ticks bite humans (see table 1).<sup>2</sup>

The description of the association between red-meat allergy and tick bites by van Nunen et al in 2007 ignited intense research interest worldwide.<sup>3,4</sup> This led to identification of the galactose-alpha-1,3-galactose (alpha-gal) antigen as the target moiety for specific IgE (identified initially in cetuximab anaphylaxis) and to a plethora of work in Asia, Europe, the US and

South Africa, resulting in a great deal of knowledge about this clinical phenomenon and confirming its cause.<sup>5-12</sup>

The spectrum of tick-induced allergies continues to widen and spans most of the different food-allergy syndromes.<sup>13,14</sup> Certain conditions appear to be caused by classical IgE-mediated reactions to specific tick salivary proteins (large local reactions to tick bites, tick anaphylaxis) while all other tick-induced allergies are likely due to IgE-mediated or T-cell-mediated reactions to the carbohydrate molecule, alpha-gal.<sup>1,2,13,14</sup>

Ticks make alpha-gal and transmit it when they inject their saliva into the human host during a blood feed.<sup>8,12</sup>

Management of a tick-induced allergy varies according to the clinical features observed or predicted as likely to occur with re-exposure,

to either the tick salivary protein or alpha-gal allergens. Management of MMA can be therapeutically complicated if the individual is highly sensitive to the allergen, alpha-gal, as this may be present in vaccines and medicines.<sup>15-21</sup>

Most individuals who develop MMA will have a significant reduction in their alpha-gal-specific IgE levels over 18 months to two years, and many will be able to tolerate mammalian meat a few years thereafter.<sup>22</sup>

The recognition of alpha-gal by the immune system is at the crossroads of defence against infectious diseases, malignancy and the development of other non-communicable diseases (apart from allergy).<sup>23,24</sup> Further sequelae of sensitisation to alpha-gal are becoming apparent – for example, an increased risk of atheroma formation and of more severe atheromatous plaques.<sup>25</sup>

Tick anaphylaxis, an IgE-mediated reaction to one of five tick salivary proteins, has become much more prevalent in this century, with fatalities recorded.<sup>1,26-28</sup>

MMA after tick bite is one of very few food allergies where the cause of developing the allergy has been identified. It is thus a preventable allergy.

Research by the authors and their colleagues (supported and/or funded by TiARA [tick-induced allergies research and awareness], see box 1) has provided evidence-based strategies for tick-bite management in the prevention of allergic reactions and for the use of repellents and permethrin-treated clothing in prevention of tick bites.<sup>29-31</sup>

This How to Treat will focus on the recognition and management of tick-bite allergies and the prevention of tick bites.

**WHAT ARE TICK-INDUCED ALLERGIES?**

THE spectrum of tick-induced allergies spans from allergies to tick salivary proteins, to the glycan (carbohydrate), alpha-gal and, less commonly, probable T-cell-mediated conditions, such as food-carbohydrate-induced enterocolitis syndrome (FCIES).<sup>2,5,13,26,27</sup> Very rarely, it also includes another putatively T-cell-mediated condition of systemic contact dermatitis responsive to mammalian meat exclusion.<sup>14</sup>

**EPIDEMIOLOGY**

**Prevalence of tick-induced allergies**

THE prevalence of MMA in the tick hyperendemic region of Northern Sydney is estimated at 113/100,000, the highest world-wide.<sup>2,19</sup> There are no available data for the prevalence of mammalian meat allergy/anaphylaxis for the remainder of Australia. Overseas estimates indicate up to 35% of the population in tick endemic regions possess alpha-gal specific IgE (sIgE) and, of these, 8-9% will express symptoms of mammalian meat allergy, particularly when amplifying factors for food allergic reactions, are operative.<sup>19,32,33</sup>

**Distribution of tick-induced allergies in Australia**

The development of tick-induced allergies depends on ticks being endemic in a locale inhabited or visited by a human host predisposed to developing these allergies when bitten by a tick.

In Australia, tick-induced allergies occur mostly along the eastern seaboard (as a result of bites from *Ixodes holocyclus*, see figure 1). Ninety-five per cent of tick bites in Australia are from *Ixodes holocyclus*.<sup>34</sup> Mammalian meat anaphylaxis has also been reported in Denmark, WA (*Ixodes (Endopalpiger) australiensis*).<sup>35</sup>

The Great Dividing Range, a geological feature running down most of the eastern coast, ensures that adequate humidity for tick survival extends 20-30km inland. Ticks flourish where the microclimate is more humid – typified by the Northern Beaches area of Sydney and Denmark, WA. The weather largely decides the numbers of nymph-stage ticks that survive to become adult ticks (see figure 2). Ticks do not survive in dry weather.

Reports of *Ixodes holocyclus* in inland localities, such as Armidale and Canberra, are likely descriptions of tick ‘travellers’ returning on human or animal hosts from visits to the coast. Depending upon the microclimate, their presence may be evanescent.

**Distribution of mammalian meat allergy worldwide**

MMA has been reported in more than 18 countries (see table 2). Several tick species, other than *Ixodes holocyclus*, have been implicated.<sup>2</sup>

Australians travelling in these countries are at risk of either contracting MMA de novo or of recharging their alpha-gal-sIgE levels.

**PATHOGENESIS**

**Large local reactions to tick bites**

THE pathogenesis of large local reactions (LLRs) to ticks is generally

**Box 1. Tick-induced allergies research and awareness (TiARA)**

- A group of eminent Australians, clinicians and researchers convened to:
- Promote awareness of tick-induced allergies to the public, health professionals, those in at-risk occupations, educators and the government.
  - Provide resources and support for those with tick-induced allergies who live in areas remote from expert medical and dietetic advisors.
  - Promote research into the prevention and cure of tick-induced allergies.
  - Disseminate established tick management strategies and help develop novel, proven tick management measures.

Source: tiara.org.au

**Table 1. Classification of tick-induced allergies**

Type	Features
Allergies (IgE-mediated reactions) to tick salivary proteins	Large local reactions to tick bites Tick-bite anaphylaxis
Allergies (IgE-mediated reactions) to the glycan, alpha gal	Delayed mammalian meat allergy/ anaphylaxis
Probable T-cell-mediated conditions (non-IgE-mediated reactions)	FCIES Systemic contact dermatitis to mammalian meat



**Figure 1. Distribution map of *Ixodes holocyclus* (Australian paralysis tick).**

considered to be due to tick salivary protein sIgE activating dendritic cells, mast cells and basophils in the skin, causing release of inflammatory mediators, as occurs in all classical allergic reactions (see figure 3).

In those who develop LLRs, late-phase inflammation, limited to the skin and mediated by Th2 cytokines (IL-5, IL-9 and IL-13) follows.<sup>36</sup>

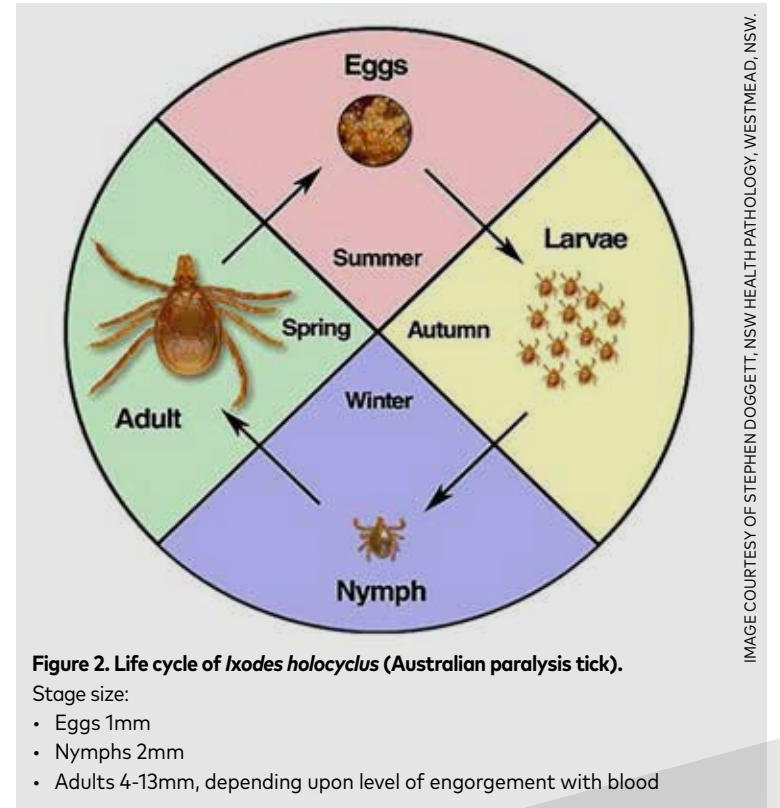
**Tick-bite anaphylaxis**

Tick-bite anaphylaxis is due to an IgE-mediated allergic reaction to

one of five tick salivary proteins injected into the host by the tick when feeding (see figure 4).<sup>26,27</sup> Bites from nymph and larval ticks may

**Only the bite from an adult tick can trigger an episode of anaphylaxis.**

prime the production of sIgE to tick salivary proteins; however, only the bite from an adult tick can trigger an episode of anaphylaxis. Crucially,



**Figure 2. Life cycle of *Ixodes holocyclus* (Australian paralysis tick).**

- Stage size:
- Eggs 1mm
  - Nymphs 2mm
  - Adults 4-13mm, depending upon level of engorgement with blood

**Table 2. Worldwide distribution of mammalian meat allergy**

Mammalian meat allergy	Countries
Mammalian meat allergy 2007: one continent	Australia
Mammalian meat allergy 2020: six continents (all continents where ticks bite humans)	Australia, US, France, Spain, Germany, Korea, Japan, Sweden, Switzerland, Panama, UK, Italy, Republic of South Africa, Brazil, Belgium, Ivory Coast, Norway, Austria, New Zealand



**Figure 3. Large local reaction to two nymph tick bites.**

the anaphylaxis does not occur until the tick has been disturbed or compressed. Because the tick injects the allergen into the circula-

**Delayed mammalian meat allergy/anaphylaxis**

Fossil records show that, about 28 millennia ago, almost all hominoids were wiped out – probably by an infectious agent, perhaps malaria – in a pandemic. Our forebears who survived had inactivated the gene for the enzyme alpha-galactosyl-transferase and therefore could not make alpha-gal.<sup>23,24</sup> This meant they could mount an effective immune response by making IgG2 directed against infectious organisms. It also means

IMAGE COURTESY OF STEPHEN DOGGETT, NSW HEALTH PATHOLOGY, WESTMEAD, NSW.

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◀ PAGE 12 that alpha-gal is now foreign to humans, and our immune system responds by making IgG1 to alpha-gal.<sup>37</sup>

Individuals with A or O blood groups are more prone to developing MMA (B and AB blood groups constitutively contain some gal).<sup>8</sup> In predisposed humans, there is a switch from IgG1 production (for protection against infectious diseases) to producing IgE-specific for alpha-gal.<sup>37-39</sup> Allergic reactions ensue when cross-reactive alpha-gal-containing foods/medications are administered to those individuals.<sup>40,41</sup>

In this century, with tick-host changes (fox baiting in Australia and white-tailed deer in the US), it is likely that more ticks are making alpha-gal in response to changes in their microbiota, and as ticks inject their saliva containing the alpha-gal, this route of administration bypasses the 'meet-and-greet' cells of the immune system (dendritic cells), resulting in the epidemic of alpha-gal sensitisation in tick-endemic areas (see figures 5A and B).<sup>39</sup>

## Probable T-cell-mediated conditions (non-IgE-mediated reactions)

### FOOD-CARBOHYDRATE-INDUCED ENTEROCOLITIS SYNDROME

In 2019, FCIES was reported in 1% of 303 people with MMA.<sup>13</sup> Characteristically, alpha-gal sIgE is not found in patients with this condition, analogous to food-protein-dependent enterocolitis syndrome (FPDES).

## Tick anaphylaxis is the most severe form of immediate tick-induced allergy.

T-cell-mediated inflammation is thought to underly the symptoms and signs.

### SYSTEMIC CONTACT DERMATITIS TO MAMMALIAN MEAT RESPONSIVE TO MAMMALIAN MEAT EXCLUSION

This condition, described in a single case in 2020, is thought to result from alpha-gal-induced T-cell-mediated inflammatory processes limited to the skin, analogous to that seen with systemic nickel contact dermatitis.<sup>14</sup>

## NATURAL HISTORY

### Tick anaphylaxis

WHEN the adult tick is killed by freezing it in situ and allowing it to detach spontaneously or is removed with fine-tipped forceps in the hands of an expert, a recurrence of tick anaphylaxis is unlikely.<sup>29,40</sup> It has not been commercially viable to translate the research demonstrating the presence of sIgE to tick salivary proteins into developing an in-vitro test to confirm tick anaphylaxis or manufacture immunotherapy. The duration of the risk of anaphylaxis to an adult tick is unknown but is likely to be many years.

### Mammalian meat allergy

Recent work noted a significant reduction in the level of alpha-gal



Figure 4. Electron microscope image of *Ixodes holocyclus* mouth parts.



Figure 5A. Adult *Ixodes holocyclus* embedded in scalp.



Figure 5B. A nymphal paralysis tick embedded behind the ear. This tick has been in place for less than two hours and is yet to swell up with blood. Behind the ears is a common place for ticks to attach, especially in children.

sIgE over 18 months to two years, and after 3-4 years many those with MMA may tolerate mammalian meats again, provided there has been no further tick bite from

any life stage (larval, nymph or adult) tick.<sup>22</sup> If an individual has developed MMA, however, and is bitten by another tick, the levels of sIgE to alpha-gal have been

shown to more than double.<sup>35</sup> Even a single tick bite (nymph or adult and possibly larval) may resensitise an individual whose MMA has remitted.

While the clinical reactivity to mammalian meats may settle, a long tail of low-level sIgE to alpha-gal occurs in many patients. The risk of reaction to parenteral sources of alpha-gal – for example, cetuximab – therefore remains.<sup>16-18,21,40,41</sup>

### T-cell-mediated conditions

The natural history of these complaints is not known.

## AETIOLOGY

ALL tick-induced allergies are caused by tick bites occurring in predisposed human hosts.

## CLINICAL PRESENTATION

ANY of the tick-induced allergies may occur at any age.

### Tick salivary protein allergies

**LARGE LOCAL REACTIONS**  
LLRs to tick bites are the least severe form of tick-induced allergy (see box 2). Any insect, most commonly mosquitoes, can trigger LLRs. The diagnosis is made clinically, and no further investigations for allergy are indicated for diagnosis.

### TICK ANAPHYLAXIS

Tick anaphylaxis is the most severe form of immediate tick-induced allergy. Australia recorded four fatalities from tick anaphylaxis between 1997 and 2013.<sup>28</sup>

The clinical presentation of tick anaphylaxis is a sudden, often severe, anaphylaxis occurring as soon as an adult tick is disturbed or compressed during removal.<sup>42</sup> The diagnosis is made clinically. A RAST for sIgE to alpha-gal may be done to identify those at risk of also developing MMA (around 30%).<sup>40</sup>

### Glycan (alpha-gal) allergies

#### MAMMALIAN MEAT ALLERGY AFTER TICK BITE

The MMA spectrum comprises delayed MMA/anaphylaxis, gut-predominant symptoms, food-carbohydrate-induced enterocolitis syndrome and systemic contact dermatitis to mammalian meat.

Classically, MMA after tick bite presents as a delayed (typically by 3-6 hours), 'middle of the night', rapidly evolving, severe anaphylaxis in an individual with a history of previous tick bite (see table 3).<sup>2,4</sup>

### Role of amplifying or cofactors

In food allergy in general, certain factors operative around the time of ingestion of the food allergen can amplify reactions. Amplifying factors are prominent modulators of allergic reactions in MMA (see box 3).<sup>19,32,33,44</sup> More than one amplifying factor may be operative in a single episode of allergy.

Individuals may be unaware of having been bitten by a tick if they do not live in a tick-hyperendemic area – for example, visiting the Northern Beaches in Sydney, NSW; Maleny in Queensland; Denmark in WA; and Lakes Entrance, Victoria – especially if bitten by a nymph-stage tick (2mm and resembling a tiny black splinter, see figure 2) or when the tick is removed without being visualised – for example, scratched out of the scalp.<sup>43</sup>

'Asymptomatic' alpha-gal sensitised individuals exist. Up to 25%

IMAGE COURTESY OF SIMON HINKLEY, KEN WALKER MUSEUMS VICTORIA

IMAGE COURTESY OF STEPHEN DOGGETT NSW HEALTH PATHOLOGY, WESTMEAD, NSW.

IMAGE COURTESY STEPHEN DOGGETT NSW HEALTH PATHOLOGY, WESTMEAD, NSW.

Table 3. Characteristics of presentations of MMA	
Condition	Features
Delayed MMA/anaphylaxis <sup>2</sup>	<ul style="list-style-type: none"> <li>• Reaction occurs typically 3-6 hours after ingesting mammalian meat</li> <li>• Classical presentation is a 'middle of the night' anaphylaxis evolving rapidly, is often severe and is due to basophil activation intravascularly</li> <li>• Previous history of tick bite/s</li> <li>• Tick-bite history may be difficult to elicit in patients from non-tick-endemic regions</li> <li>• Anaphylaxis symptoms are as for anaphylaxis in general except for the delay in symptom appearance</li> <li>• Delay is due to absorption time for the glycolipid allergen from the gut into intestinal lymphatics and then the inferior vena cava to activate basophils in the circulation, thus triggering the anaphylaxis</li> <li>• Anaphylaxis treatment is non-specific (as for any anaphylaxis)</li> <li>• A minority of individuals who have had an anaphylaxis to mammalian meats will also react to mammalian milk and its products (eg, react to soft cheeses but tolerate hard cheeses and be intolerant of non-Australian cheeses containing animal rennet)</li> <li>• MMA may present as an anaphylaxis to gelatine (particularly parenterally administered)<sup>42</sup></li> <li>• Appearance typical for urticaria and angioedema</li> <li>• Lesions of angioedema may occur at the site of previous tick bites</li> </ul>
Gut-predominant constellation of symptoms	<ul style="list-style-type: none"> <li>• Nausea may precede abdominal pain</li> <li>• Colicky abdominal pain features</li> <li>• Diarrhoea is common</li> <li>• Often occurs within an hour</li> <li>• Urticarial lesions and patchy erythema may be present concomitantly</li> <li>• Antihistamines and corticosteroids not helpful usually</li> <li>• Adrenaline not indicated and no improvement in gut symptoms seen if used</li> </ul>
Food-carbohydrate-induced enterocolitis syndrome <sup>13</sup>	<ul style="list-style-type: none"> <li>• Affects an estimated 1% of mammalian meat reactors<sup>13</sup></li> <li>• Symptoms as for FPIES</li> <li>• Protracted severe vomiting and diarrhoea feature</li> <li>• Hypotension often occurs (due to the fluid phase shift from the circulation to the gut)</li> <li>• Pallor and lethargy typical (in contrast to IgE-mediated reactions where erythema is usual)</li> <li>• Alpha-gal sIgE convincingly negative (as for FPIES with other foods)</li> <li>• Not an IgE-mediated condition (attributed to T cell-mediation)</li> </ul>

Table 4. Differential diagnoses	
Condition	Differential diagnoses
LLRs to tick bites	Cellulitis
Tick anaphylaxis (The rapid onset of the anaphylaxis very soon after the adult tick is disturbed or compressed during its removal is pathognomonic)	Anaphylaxis triggered by another agent, eg, bites from other insects, drugs or foods
FCIES	Single episode is any cause of severe vomiting or diarrhoea: acute gastroenteritis, medication, migraine, pregnancy, toxins (alcohol) or cholelithiasis Recurrent episode, where a hot shower relieves the vomiting, consider cannabinoid hyperemesis syndrome
Systemic contact dermatitis responsive to mammalian meat exclusion	Other causes of systemic contact dermatitis, eg, nickel

**Box 4. Tick removal mantra for the community**

**If you live, work, volunteer or play where ticks live**

- Do not scratch anything you can't see.
- Do not disturb a tick.
- Kill the tick where it is.

**For ticks you can hardly see (larval and nymph-stage ticks)**

- "Dab it, don't grab it!" (Apply permethrin cream), for example, Lyclear

**For ticks you can see (adult ticks)**

- "Freeze it, don't squeeze it!" (Use an ether-containing spray without a "bookmask"), for example, Tick Off (see figure 6).
- And please remember: "Household tweezers are tick squeezers."

tiara.org.au; allergy.org.au

**Box 2. Clinical features of LLRs to ticks**

- Large areas of induration (5cm x 5cm or greater) at the site of a tick bite.
- Occur with nymph-stage or adult tick bites.
- Start within 4-12 hours of being bitten.
- Attain maximum size by 48-72 hours.
- Can be extensive, involving at least the joint above or below the swelling.
- Often incapacitating.
- Resolve completely within 7-10 days.
- As they resolve, swellings move downwards because of gravity.
- Respond well to antihistamines and oral corticosteroid given early.

of the population in a tick hyperendemic region may be sensitised but not clinically reactive to mammalian meats.<sup>19</sup> Up to 50% of individuals may be sensitised to alpha-gal after two tick bites.<sup>45</sup>

There is a 95% probability that individuals with alpha-gal-sIgE levels of 5.5kU/L or greater will have symptomatic MMA following mammalian meat ingestion in the absence of amplifying factors.<sup>10</sup> In those with alpha-gal sIgE levels less than 5.5kU/L, approximately two-thirds will have symptoms with ingestion of mammalian meats (Dr van Nunen personal communication 2020). However, they require the presence of amplifying/cofactors to express their allergy to mammalian meats or meat products.

Uncommonly, alpha-gal sensitised patients will present with reactions to gelatine, such as in vaccines, or to medications, for example, cetuximab.<sup>6,16-18, 41,42</sup>

**DIFFERENTIAL DIAGNOSES**

THE differential diagnoses appear in table 4.

**MANAGEMENT**

PATIENT education regarding evidence-based tick-bite prevention and management is essential.

Prevention includes dressing appropriately when gardening and treating the backyard.

**Box 3. Factors that may amplify MMA reactions**

- Greater amount of mammalian meat or meat product consumed.
- Alcohol consumed concomitantly.
- Sleep deprivation.
- Exercise (reaction within two hours either side of the food being consumed).
- Effect of cooking in liberating the alpha-gal allergen (slow-cooked more so than reheated more so than raw meats).
- Use of spice, especially chilli (all except nutmeg, black pepper, bay leaf).
- NSAIDs prior.
- Recently being unwell (eg, URTI).
- Perimenstrual phase when applicable.

Some amplifying factors may bring forward the timing of the onset of an individual reaction as well.

Box 4 and figures 6 and 7 outline tick removal strategies.

**Large local reactions to tick bites**

Management at presentation comprises elevation of the tick-bitten area above the heart, application of

IMAGE COURTESY OF RENEE NOWYTAGGER FOR TIARA



Figure 6. Ether spray freezing technique.

«ice, early use of antihistamines (to be continued for 7-10 days depending on symptoms of pruritus) and a short course of moderate-dose corticosteroids (for example, 50mg prednisolone for an adult, daily for three days) ideally early in the 72-hour evolution phase of the LLR. A single dose of oral dexamethasone (4mg) in the ED will cover 72 hours, no prescription is needed and medication compliance is assured.

LLRs may be indistinguishable from cellulitis. When these reactions involve the periorbital area, a condition more common in the paediatric population, treatment includes antihistamines and oral antibiotics, and close and regular follow-up. Tetanus toxoid vaccine may be indicated if the last booster was more than 10 years earlier.

At follow-up, advise the patient to keep an antihistamine and a suitable first dose of oral corticosteroid available as 'pills in a pocket' because early introduction of these may limit the extent of any subsequent LLR to a tick bite and reduce the possibility of requiring antibiotics.

**Mammalian meat exclusion is only recommended if symptoms occur after ingestion of mammalian meat.**

Unless the LLRs are progressively increasing markedly in size, indicating a greater risk of systemic reaction, provision of an adrenaline autoinjector is not usually necessary.

**Tick anaphylaxis**

Management of tick anaphylaxis is the same as for anaphylaxis from any other cause. First-aid measures include lying the patient down (if not too breathless); if breathless, sit them up on the ground/floor; call 000; give salbutamol if the patient is asthmatic and experiencing shortness of breath and administer an adrenaline autoinjector if available and if symptoms and signs warrant. Check the tick has been killed and removed, and check the patient for the presence of other adult ticks.

Long-term management of tick anaphylaxis is to prevent tick bites from all life stages and to manage any tick bite using the Australian evidence-based techniques. If an adult tick bite occurs in a known tick anaphylaxis patient, leave the tick undisturbed, call 000 and take the patient to the nearest ED. In the authors' opinion, green tweezers issued to ambulance officers should not be used as they are likely to disturb the tick. Encourage the patient to enter the information in her/his My Health Record, especially if they have sIgE to alpha-gal.

Larval and nymph ticks should be killed in situ with permethrin cream, and these can be treated at home.

**Mammalian meat allergy after tick bite**

MMA management involves determining whether any mammalian meat product can be consumed safely

and the timing of any reintroductions. A baseline alpha-gal sIgE is essential. Stratify the risk of reaction for the patient (using the alpha-gal sIgE level) and establish which meats or mammalian products are likely to be tolerated. When symptoms are occurring with non-meat sources of alpha-gal, a diet history and symptom log will reveal the culprit/s. Discussion of the role of amplifying factors is a crucial safety measure.

If symptoms or signs warrant, prescribe an adrenaline autoinjector by authority (with the support of an immunologist/allergist if necessary), demonstrate its use, discuss its indications and contraindications for use and complete an anaphylaxis action and travel plan.

Encourage the patient to enter the information in her/his My Health Record. Follow progress at intervals.

Ensure the patient is aware that, for many with MMA, if no further tick bites of any life stage occur, the MMA can remit over 3-4 years. If further tick bites occur, these can result in the alpha-gal sIgE levels more than doubling. Discuss the implications of sensitisation to alpha gal. A mammalian meat-free diet, dietary iron resource and chef card are available online at www.tiara.org.au.

Consider review by a dietitian and counselling if the patient has had a severe anaphylaxis.

**T-cell-mediated conditions FOOD-CARBOHYDRATE-INDUCED ENTEROCOLITIS SYNDROME**

Management of FCIES to mammalian meat involves avoidance of mammalian meat. The absence of alpha-gal sIgE is confirmatory when the history is typical.

**SYSTEMIC CONTACT DERMATITIS TO MAMMALIAN MEAT**

Management of this condition is avoidance of mammalian meat and mammalian products.

**CASE STUDIES**

**Case study one**

JIM, 74 and retired, is brought by ambulance to the ED at Northern Beaches Hospital, Sydney, NSW, after collapsing while having afternoon tea with friends nearby. At the scene, paramedics noted his blood pressure was initially unrecordable. His friends had said they had been gardening earlier. Jim had not complained that afternoon, enjoyed good health and had taken an NSAID after morning golf.

With Jim placed flat on the ground and his legs elevated, consciousness returns sufficiently for him to give a history of starting to feel lightheaded moments after he pulled a tick out of

his neck using his fingers. A repeat recumbent blood pressure is 70/50, so the paramedics administer adrenaline 0.5mg IM and oxygen. A second dose of adrenaline 0.5mg and 500mL IV saline are administered before transfer to the ED.

In the ED, he develops generalised urticaria. His vital signs remain stable, so no further adrenaline is required; antihistamine and hydrocortisone are administered. Full-body examination fails to reveal any other ticks.

Jim has a history of previous tick bites after bushwalking on the NSW South Coast. These resulted in slight swelling at the bite site only. With help from the TiARA pamphlet, 'Preventing and managing tick bites', he identifies the previous ticks as having been nymphs and the tick he pulled out as an adult. Jim is educated in evidence-based tick-bite prevention and management

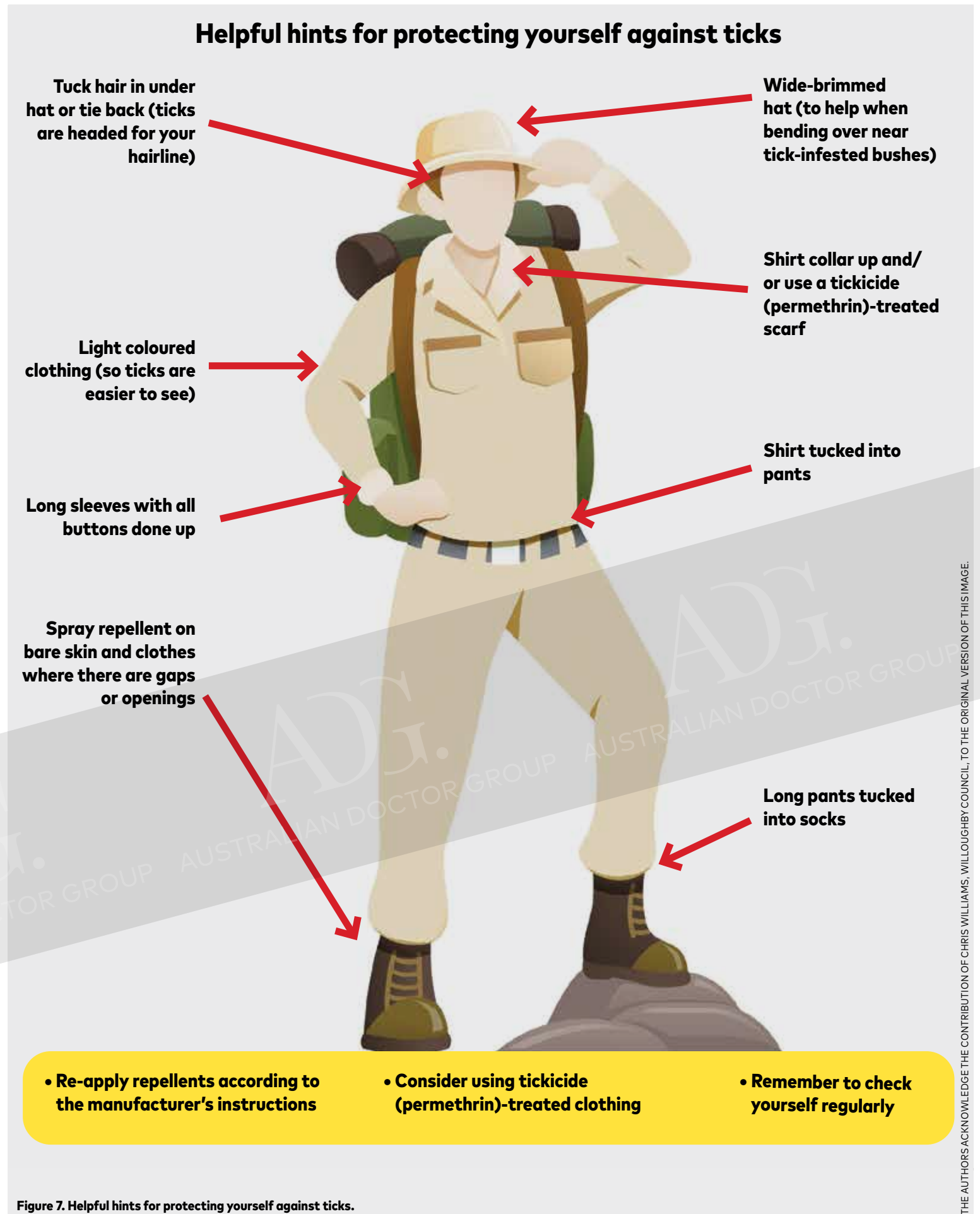


Figure 7. Helpful hints for protecting yourself against ticks.

THE AUTHORS ACKNOWLEDGE THE CONTRIBUTION OF CHRIS WILLIAMS, WILLOUGHBY COUNCIL, TO THE ORIGINAL VERSION OF THIS IMAGE.

◀ PAGE 16 techniques, given an adrenaline autoinjector and shown how to use it. Jim is given ADT as he has not had a tetanus toxoid vaccination for more than 10 years.

In view of the severity of Jim's anaphylaxis, a tryptase level is requested, and in the discharge summary the ED consultant asks his GP to follow up on this.

The following day Jim sees his inner Sydney GP, who completes an anaphylaxis action and travel plan and gives Jim information about obtaining a personal medical warning device, as he is a keen coastal trekker.

Physical examination reveals no complication at the site of the tick bite, blood pressure is 130/85 and ECG is normal. Jim has researched tick anaphylaxis online and asks if he should continue to eat mammalian meat. His GP suggests a RAST for alpha-gal-specific IgE, which is elevated at 4.6kU/L (less than 0.35kU/L is negative). The tryptase level is elevated at 25µg/mL (normal less than 11.4µg/mL).

Jim's GP has not managed a patient with tick anaphylaxis previously so seeks information from [www.allergy.org.au](http://www.allergy.org.au) (Australasian Society of Clinical Immunology and Allergy) and recommends review by a clinical immunologist/allergist.

Jim is reviewed urgently by the clinical immunologist/allergist who explains that an elevated alpha-gal sIgE occurs in around 70% of individuals with tick anaphylaxis; however, only around 30% go on to develop symptoms of MMA (Personal

communication Dr van Nunen 2020). Thus, mammalian meat exclusion is only recommended if symptoms occur after ingestion of mammalian meat. As Jim had experienced one anaphylactic episode, he had decided it was prudent to cease eating mammalian meat until reviewed by the allergist. He is now advised to reintroduce mammalian meat gradually, starting with mammalian meat products least likely to provoke a reaction.

Ramifications of sensitisation to alpha-gal are explained to Jim: therapeutic (possible reactions to certain vaccines and heparin) and, noting his coastal trekking, to snake antivenoms.

Jim is advised to make any attending health professional aware of his alpha-gal sensitisation and encouraged to upload documentation to his My Health Record.

He is informed the alpha-gal sIgE should reduce significantly over the next two years. He is given a pathology request form to check progress in six months and at intervals thereafter depending upon the rate of decline of the alpha-gal sIgE.

A convalescent tryptase level is normal, eliminating coexisting mastocytosis. Tick-bite prevention and management strategies and the use of the adrenaline autoinjector are reinforced.

Jim is informed that his tick anaphylaxis is due to an allergy to a tick salivary protein and not the carbohydrate alpha-gal and that there is no test yet available for tick anaphylaxis.

Because of concerns regarding transmission of infection (for example, Rickettsiosis) and the lack of commercial viability, it is unlikely that immunotherapy for tick anaphylaxis will become available in the near future.

Jim is also told that only an adult tick is capable of causing an anaphylaxis and that research shows a recurrence of his tick anaphylaxis is most unlikely, provided the tick bite is managed properly: do not disturb the tick, call 000, be transferred to the nearest ED where the tick will be frozen and then removed expertly using fine-tipped forceps. As he is sensitised to alpha-gal, bites from all tick stages should be avoided. He is advised to return if he develops MMA. One year later, he has another adult tick bite, which was successfully killed in situ (frozen) and removed in the ED. Jim continues to tolerate mammalian meat.

## Case study two

Kelly, 38, lives near Maleny in the Sunshine Coast hinterland, Queensland. She presents to her GP with recurrent episodes of urticaria. Questioning reveals these episodes occur at about midnight and are worsening over time. Kelly kept a dietary and symptom diary for the month during which the past two episodes occurred, and this reveals that on each occasion mammalian meat was consumed at dinner with a glass of wine. On other occasions, mammalian meat was consumed without alcohol and urticaria did not occur.

When prompted, Kelly recalls one episode when no wine was consumed and she had eaten reheated spaghetti bolognese, which she had tolerated earlier that week.

The latest episode involved mild tongue swelling, and she reported feeling dizzy momentarily when getting out of bed to find an antihistamine.

Several tick bites had occurred since Kelly moved to Maleny. Her lifetime number of tick bites was 10, all of which had been nymph bites. The life stage was identified at an earlier presentation for a local reaction to the nymph tick bite, which had then become infected after the family dog had licked it. An alpha-gal sIgE is 4.2kU/L (less than 0.35kU/L is negative). Her GP prescribes an adrenaline autoinjector after a telephone consultation with a clinical immunologist/allergist, demonstrates the use of the device and discusses the indications and contraindications. The GP completes an anaphylaxis action plan and a travel plan and shows Kelly a video of evidence-based tick-bite prevention and removal techniques.

Unfortunately, Kelly has a further tick bite and starts to have delayed reactions (3-6 hours after consumption) each time she eats mammalian meat. RAST shows an alpha-gal sIgE increase to 8.9kU/L (less than 0.35kU/L is negative). She is advised to exclude mammalian meat and tick-bite prevention and management advice is reinforced. Kelly is told about dietary iron sources and

downloads a 'chef's card' for eating out ([www.tiara.org.au](http://www.tiara.org.au)).

The GP tells Kelly that, provided she has no further tick bites, the alpha-gal sIgE should reduce over the next 18 months to two years and she may be able to eat mammalian meat in 3-4 years.

Six months later, when out walking her dog, Kelly fractures an ankle and requires alpha-gal-free analgesia, anaesthesia, surgery and anticoagulant. The clinical immunologist/allergist liaising with the treating team ensures the ankle surgery avoids the use of alpha-gal-containing substances and medications.

## CONCLUSION

TICK-INDUCED allergies, chiefly MMA and tick anaphylaxis, are emergent and occasionally lethal. The spectrum of tick-induced hypersensitivity reactions encompasses both IgE- and probable T-cell-mediated phenomena.

Our current understanding of MMA is that it arises from the interplay between genetic, epigenetic and environmental factors, resulting in formation of alpha-gal sIgE. Its clinical expression is determined by the presence or absence of amplifying factors for food allergic reactions, together with the constitutional ability of an individual's immune system to modulate its reactivity to allergens.

Sensitisation to alpha-gal, even in the absence of clinical reactivity to mammalian meat, confers a risk of allergic reactions to a range of therapeutic agents and the likely development of other non-communicable, non-allergic diseases.

Tick-induced allergies are among the most easily preventable. Killing the tick in situ (for example, freezing an adult tick) and, if necessary, expertly removing the dead tick by using fine-tipped forceps is proven to reduce allergic reactions and is the standard of care in 2020.

Given the novelty and complexity of tick-induced allergies, consider specialist referral if in any doubt as to the diagnosis, interpretation of investigations or the implications and long-term management.

## RESOURCES

- **Tick-Induced Allergies Research and Awareness** [tiara.org.au](http://tiara.org.au)
  - **Tick Anaphylaxis and Mammalian Meat Allergy Resources:** [bit.ly/38m32aQ](http://bit.ly/38m32aQ)
  - **Video of tick bite prevention and removal techniques:** [tiara.org.au](http://tiara.org.au)
  - **Mammalian meat and mammalian product free dietary resources:** [bit.ly/2VFu8Eq](http://bit.ly/2VFu8Eq)
- **The Australasian Society of Clinical Immunology and Allergy** [allergy.org.au](http://allergy.org.au)
- **Allergy and Anaphylaxis Australia** [allergyfacts.org.au](http://allergyfacts.org.au)
  - **Chef's card template:** [bit.ly/2ZttET5](http://bit.ly/2ZttET5)
- **University of Sydney department of medical entomology:** [bit.ly/3gZsbuN](http://bit.ly/3gZsbuN)
- **NSW Health Agency for Clinical Innovation Patient factsheet Tick Management** [bit.ly/2Wk4aa1](http://bit.ly/2Wk4aa1)

References on request from [howtotreat@adg.com.au](mailto:howtotreat@adg.com.au)

## How to Treat Quiz.

TICK-INDUCED MAMMALIAN MEAT ALLERGY AND TICK ANAPHYLAXIS



GO ONLINE TO COMPLETE THE QUIZ [ausdoc.com.au/howtotreat](http://ausdoc.com.au/howtotreat)

### 1. Which THREE statements about tick-induced allergies are correct?

- a Tick-induced allergies include tick anaphylaxis.
- b Tick-induced allergies include MMA.
- c Tick-induced allergies have never been fatal.
- d Tick-induced allergies include probable non-IgE-mediated gut reactions.

### 2. Which THREE statements about MMA are correct?

- a MMA occurs after a previous tick bite.
- b MMA reactions typically occur minutes after eating meat.
- c MMA is an IgE-mediated reaction.
- d MMA may develop at any age.

### 3. Which TWO statements about tick anaphylaxis are correct?

- a Tick anaphylaxis only occurs with adult tick bites.
- b Tick anaphylaxis is never fatal.
- c Tick anaphylaxis starts only when the tick is disturbed.
- d Tick anaphylaxis occurs with nymph or larval tick bites.

### 4. Which THREE statements about MMA are correct?

- a MMA persists throughout life even if no more tick bites occur.

- b MMA may remit if no more tick bites occur.
- c MMA does not necessarily cause an allergic reaction every time meat is consumed.
- d Amplifying/cofactors are important in triggering reactions to mammalian meat.

### 5. Which TWO statements about tick anaphylaxis are correct?

- a People experiencing tick anaphylaxis need to remove any tick immediately with tweezers.
- b Done properly, freezing adult ticks kills them instantly and avoids allergic reactions.
- c Patients with known tick anaphylaxis need medical supervision for adult tick removal.
- d A previous less severe reactions always occur before a tick anaphylaxis.

### 6. Which THREE statements about alpha-gal-specific IgE testing are correct?

- a Detection of alpha-gal sIgE is useful for a patients in confirming a diagnosis of MMA.
- b Detection of alpha-gal sIgE is

useful in stratifying the risk of reaction in MMA.

- c Progress alpha-gal sIgE estimations are useful in advising patients of their current risk.
- d Detection of alpha-gal sIgE is unnecessary in managing MMA.

### 7. Which THREE statements about amplifying factors for allergic reactions are correct?

- a Amplifying factors/cofactors are not important in allergic reactions in MMA.
- b Known amplifying factors in MMA include alcohol, exercise and prior NSAID use.
- c Interpreting meat challenge results in MMA is difficult if amplifying factor/s absent.
- d Amplifying factors in MMA include fatty dishes, reheating and slow cooking.

### 8. Which THREE statements about tick-bite prevention are correct?

- a Tick bites may be prevented by having your backyard treated.
- b Tick bites may be prevented

- by using DEET-containing insect repellents.
- c Tick bites may be prevented by wearing suitable clothing.
- d Tick bites cannot be prevented.

### 9. Which THREE statements about tick-bite management are correct?

- a Ticks should be killed in situ.
- b Ticks may be removed by using fine-tipped forceps after being killed in situ.
- c Ticks should be removed as quickly as possible even if this disturbs them.
- d Ticks near eyes or genitalia, or in those aged under four, should not be frozen in situ

### 10. Which THREE are absolute indications for referral of a tick-induced allergy patient to a specialist?

- a An LLR to a tick bite in the absence of the patient seeking a referral.
- b Any doubt as to the correct diagnosis of MMA or other tick-induced allergy.
- c Any doubt as to the long-term management of a patient with a tick-induced allergy.
- d A patient with no evidence for sIgE to alpha gal with gut symptoms.



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