Australian Government
Department of Health and Aged Care

Guidance Note for medical practitioners and hospitals

Tick-induced allergies: tick anaphylaxis and mammalian meat allergy/anaphylaxis

Tick-associated toxicosis and paralysis

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Contents

Figure

List of abbreviations

Abbreviations	Descriptions
A&AA	Allergy & Anaphylaxis Australia
AAAAI	American Academy of Allergy, Asthma and Immunology
ABS	Australian Bureau of Statistics
ACEM	Australasian College of Emergency Medicine
AGS	Alpha-gal syndrome
ANZAAG	Australian and New Zealand Anaesthetic Allergy Group
ANZCOR	Australian and New Zealand Committee on Resuscitation
ASCIA	Australasian Society of Clinical Immunology and Allergy
BATS	Basophil activation tests
CICM	College of Intensive Care Medicine of Australia and New Zealand
COVID 19	Coronavirus
CT	Computerized tomography
DSCATT	Debilitating Symptom Complexes Attributed to Ticks
ED	Emergency departments
FCIES	Food carbohydrate-Induced enterocolitis syndrome
FGF	Fibroblast growth factor
FPIES	Food protein-induced enterocolitis syndrome
HGF	Hepatocyte growth factor
IgE	Immunoglobulin E
ILCOR	International Liaison Committee on Resuscitation
IM	Intramuscularly
IV	Intravenous
MMA	Mammalian meat allergy
NCIS	National Coronial Investigation System
PDGF	Platelet-derived growth factor
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RAS	Radioallergosorbent
sIgE	specific Immunoglobulin E
TGA	Therapeutic Goods Administration
TGF	Transforming growth factor
TiARA	Tick-induced Allergies Research and Awareness
VZ	Varicella (chickenpox)
WAO	World Allergy Organisation

About this Guidance Note

Purpose and objective

This Guidance Note is part of a series of Guidance Notes on ticks, tick-borne diseases, tick-induced allergies and Debilitating Symptom Complexes Attributed to Ticks (DSCATT).

In response to the 2016 Senate Community Affairs References Committee's Final Report Inquiry into the growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients, the Australian Government commissioned the development of educational and awareness materials related to DSCATT, as well as a clinical pathway and multidisciplinary care model to support clinicians' decision-making on differential diagnosis and referral pathways for patients presenting with DSCATT. The purpose of the Guidance Notes is to provide evidence-based guidance for clinicians in community and hospital settings, as well as providing a reference source on DSCATT topics.

Topics covered in this Guidance Note

This Guidance Note covers the evidence on the currently recognised severe tick-induced allergies: tick anaphylaxis and mammalian meat allergy/anaphylaxis, and on mild allergic reactions from tick bites. It also covers the evidence on tick-associated toxicosis and paralysis.

While this Guidance Note covers allergies, anaphylaxis and paralysis associated with ticks internationally, it mostly focusses on Australian tick-induced allergies and paralysis, the vast majority of which are associated with the Australian paralysis tick (*Ixodes holocyclus*). This Guidance Note also includes some of the information in the *Prevention and management of tick bites in Australia* Guidance Note, particularly the advice that is directly relevant to the focus of this Guidance Note. These sections are 'First aid for tick-induced anaphylaxis', and 'Management of tick bites in people who are allergic to tick bites'. Specific to this Guidance Note is reference to the Australasian Society of Clinical Immunology and Allergy (ASCIA) Guidelines for acute management of anaphylaxis, including tick-anaphylaxis. Tick-induced allergies and tick paralysis are largely avoidable by preventing tick bites and safely managing tick bites. See the Guidance Note on *Prevention and management of tick bites in Australia.* Detailed information about ticks, Australian ticks, and tick-borne diseases and illnesses, and some important concepts about ticks, is covered in the *Introduction to ticks, tick-borne diseases and tick-borne diseases and illnesses* Guidance Note. Detail on Australian tick-borne diseases is provided in the *Australian endemic tick-borne diseases* Guidance Note.

This Guidance Note is based on information freely available to the public, from published peer-reviewed literature, and Australian and international guidance and guidelines, with a focus on literature published in the past 10 years. In this Guidance Note, where published peer-reviewed papers were not freely available to the public but are of high importance as they relate to the Australian situation, this literature was included. Studies and publications cited by the authors of articles included in this Guidance Note are provided as in-text citations. This approach allows for articles published outside of the past 10 years and articles that are not freely available to the public to be acknowledged and provides easy access for readers who may wish to explore an article further.

In this Guidance Note and in the series of Guidance Notes on ticks, tick-borne diseases, tick-induced allergies and DSCATT, there is some repetition of content between the Guidance Notes and also within the Guidance Notes, where appropriate. This approach enables each Guidance Note to be read as a stand-alone document, rather than requiring the reader to read from start to finish. The repetition between sections within a Guidance Note allows the reader to read each section as a standalone section, rather than being referred to other sections within the Guidance Note. The Contents page of each Guidance Note is hyperlinked to sections within the Guidance Note to enable the reader to easily access information. Additionally, readers are also referred to other Guidance Notes in this series where additional information can be found.

A short video on how to remove a tick by killing the tick *in situ* with ether-containing sprays is available here:

Important! Watch this video about how to safely remove a tick[1]
https://www.allergy.org.au/patients/insect-allergy-bites-and-stings

[1] An allergy project supported by the National Allergy Strategy, Australasian Society of Clinical Immunology and Allergy (ASCIA), Allergy & Anaphylaxis Australia (A&AA), and Tick-induced Allergies Research and Awareness (TiARA).

Overview and summary

This Guidance Note covers the evidence on the currently recognised severe tick-induced allergies: tick anaphylaxis and mammalian meat allergy/anaphylaxis, and on mild allergic reactions from tick bites. It also covers the evidence on tick-associated toxicosis and paralysis.

A range of short videos including on 'Signs and symptoms of allergic reaction', 'EpiPen® administration', and 'Anapen® administration', from Allergy & Anaphylaxis Australia (A&AA), are available here:

> For information by A&AA https://allergyfacts.org.au/resources/videos-from-a-aa

In Australia, most tick bites pose no medical problems if the tick is safely removed. Tick bites can lead to a variety of illnesses in patients, with the most common being allergic reactions. In some cases, people can experience severe allergic reactions (anaphylaxis) or mammalian meat allergy/anaphylaxis, or rarely, tick-induced paralysis (Australasian Society of Clinical Immunology and Allergy, 2019; Australian Government Department of Health, 2015; Graves & Stenos, 2017; Rappo et al., 2013; Taylor et al., 2019; van Nunen, 2018).

Tick-induced allergies are emergent and were rarely seen in the Australian population until about 2003 (Tick-induced Allergies Research and Awareness, 2019; van Nunen, 2018). A severe allergic reaction following a tick bite, MMA, was first described in 2007, and another related allergy, Food Carbohydrate-Induced Enterocolitis Syndrome (FCIES), was only described in 2019, with both allergies first described in Australia.

Tick-related allergies are the reason many people present to hospital emergency departments (ED) in regions where ticks are hyperendemic (van Nunen & Ratchford, 2021). A two-year survey of a New South Wales hospital ED found over 550 presentations of tick bite, with 34 tick bites resulting in anaphylaxis, and over 75% of these requiring adrenaline use (Rappo et al., 2013).

Mammalian meat allergy (MMA) and tick anaphylaxis are the most serious tick-induced allergies; they are often severe and are largely avoidable through prevention of tick bites and safe management of tick bites (see *Prevention and management of tick bites in Australia* Guidance Note for information about preventing, and safely managing, tick bites).

Worldwide, Australia has the highest proportion of its population affected by MMA and tick anaphylaxis (Tick-induced Allergies Research and Awareness, 2019). The Australian paralysis tick (*Ixodes holocyclus*) (see Figure 1 overleaf), a tick to which over 50% of the Australian population are potentially exposed, is capable of causing severe allergic reactions, including MMA and tick anaphylaxis (Tick-induced Allergies Research and Awareness, n.d.-b, 2019; van Nunen, 2018; van Nunen & Ratchford, 2021). The Australian paralysis tick is also capable of causing paralysis in humans (Australian Government Department of Health, 2015; Graves & Stenos, 2017; Hall-Mendelin et al., 2011). The Australian paralysis tick is the most important and medically significant tick in Australia and is responsible for over 95% of tick bites in humans in eastern Australia (Australian Government Department of Health, 2015; Geary et al., 2021; Taylor et al., 2019; van Nunen & Ratchford, 2021) and for most tick-borne illnesses in Australia (Australian Government Department of Health, 2015).

Figure 1: Questing female Australian paralysis tick (Ixodes holocyclus) (Public domain)

Public domain: S.L. Doggett, Department of Medical Entomology, New South Wales Health Pathology

https://www1.health.gov.au/internet/main/publishing.nsf/650f3eec0dfb990fca25692100069854/ea2fa455f96f36f1ca257c3700786bcb/WebPageBody/0.5510?OpenElement&FieldElemFormat=gif

Anaphylaxis, including tick anaphylaxis, is a **potentially life threatening**, severe allergic reaction that requires **immediate treatment with adrenaline** (epinephrine). **Anaphylaxis should always be treated as a medical emergency** (Australasian Society of Clinical Immunology and Allergy, 2021b). While the severity of the anaphylactic reaction can range from Mueller grade I to IV, Australian research found 74% of reactions in tick anaphylaxis to be grade IV (van Nunen et al. (2014) in Taylor et al., 2019), the most severe grade of reaction.

Worldwide, tick anaphylaxis occurs most commonly in Australia, and is becoming increasingly prevalent [here] (van Nunen (2015), van Nunen (2014), and Rappo et al. (2013) in van Nunen, 2018).

Tick anaphylaxis is only seen with bites from adult ticks, and only when the adult tick is disturbed by inappropriate handling (van Nunen (2015), van Nunen (2014), Rappo et al. (2013), Gauci et al. (1988), Broady (2013), Dorey (1998), Padula (2008), Commins & Plats-Mills (2011), Kemp (1986), Brown & Hamilton (1998), and van Nunen (2014) in van Nunen, 2018).

Anaphylactic reactions to tick bites have been fatal, but are rare (Tick-induced Allergies Research and Awareness, n.d.-b), with four deaths due to tick anaphylaxis having occurred in Australia between 1997 and 2013 (McGain et al. (2016), and Mullins et al. (2016) in van Nunen, 2018; Mullins et al. (2016), and McGain et al. (2016) in van Nunen & Ratchford, 2021).

See section on ‘Anaphylaxis caused by tick bites’ for more detail.

MMA (also called α-gal or alpha-gal syndrome (AGS), alpha-gal allergy, or red meat allergy) is a **serious, potentially life-threatening allergic reaction** which may occur after people eat red (mammalian) meat or are exposed to other products containing alpha-gal, and occurs after tick bite. The alpha-gal molecule has been identified in the saliva of certain species of ticks (Centers for Disease Control and Prevention, 2020; Fischer et al. (2020) in van Nunen & Ratchford, 2021).

Australian allergic diseases physicians were the first to describe a link between tick bites and the development of MMA. These findings have since been confirmed by researchers in the United States (US) and Europe (Australasian Society of Clinical Immunology and Allergy,

2019b; van Nunen, 2018) and also in Asia, Central and South America, and Africa; that is, on all continents where humans are bitten by ticks (van Nunen, 2018). In Australia, the locations of previous reports of MMA after tick bite have correlated with the distribution of *I. holocyclus* (Kwak et al., 2018; van Nunen, 2015). With the more recent description of *Ixodes* (*Endopalpiger*) *australiensis* as the second tick species as a cause of MMA in Australia, potential exposure of the Australian population to ticks associated with MMA has increased to about 60% (Tick-induced Allergies Research and Awareness, 2019).

MMA is due to an immunoglobulin E (IgE)-mediated reaction to an allergen, a carbohydrate moiety, alpha-gal (galactose-α-1,3-galactose) in mammalian meat (Tick-induced Allergies Research and Awareness, 2019; Commins et al. (2009) in van Nunen, 2018). On the other hand, tick anaphylaxis is an allergy to a tick salivary protein (Tick-induced Allergies Research and Awareness, 2019). While each of these reaction types relies on IgE mediation, tick anaphylaxis and MMA present quite differently clinically.

MMA symptoms often do not commence until a few weeks after the tick bite(s). While clinical findings range from angioedema or gut symptoms alone to life-threatening anaphylaxis, severe allergic reactions are more common at 65.5% (Fischer et al. (2016), and Kennedy et al. (2013) in van Nunen, 2018). Clinical and other features of MMA after tick bite include:

- patients with a history of tick bites present with allergic reactions after ingesting mammalian meat (or meat products) – reactions are typically delayed (i.e. “middle of the night” anaphylaxis) and often severe (van Nunen et al. (2009), Nuñez et al. (2011), Lee et al. (2013), Seklya et al. (2012), Hamsten, Tran et al. (2013), Michel et al. (2014), Wickner & Commins (2014), Fischer et al. (2016), Kennedy et al. (2013), Renaudin et al. (2012), Hamsten, Starkhammar et al. (2013), Fischer et al. (2015) in van Nunen, 2018). The anaphylaxis that evolves rapidly and is often severe is due to intravascular basophil activation (Crispell et al. (2019) in van Nunen & Ratchford, 2021)
- the interval between mammalian meat ingestion and allergic reaction is two to 10 hours, usually three to six hours depending on exposure to co-factors/amplifying factors (e.g. alcohol or exercise) (Commins et al. (2009), Jacquenet et al. (2009), Fischer et al. (2016), Renaudin et al. (2012), Morisset et al. (2012), Morisset et al. (2013), and Fischer et al. (2015) in van Nunen, 2018)
- anaphylaxis can occur in up to 60% of patients (van Nunen et al. (2007), van Nunen et al. (2009), Commins et al. (2009), Nuñez et al. (2011), Hamsten, Tran et al. (2013), Wickner & Commins (2014), Shepherd (2015), Calamari et al. (2015), Fischer et al. (2016), Kennedy et al. (2013), Renaudin et al. (2012), and Hamsten, Starkhammar et al. (2013) in van Nunen, 2018).
- In people with MMA, there is a history of tick bite. Occasionally, evidence for the tick bite can be obscure or subtle (e.g. a recalled excoriated scalp lesion consistent with a tick bite after only a single visit to a tick endemic area) (van Nunen et al. (2013) in van Nunen, 2018). In MMA, even a single bite from either nymphs or adult ticks can provoke the condition (van Nunen, 2018). Finding the association between tick bites and the development of MMA has proven to be the lynchpin in the prevention of MMA (Tick-induced Allergies Research and Awareness, 2019).

Management of MMA includes dietary education, therapeutic precautions, prevention of tick bites, and killing the tick *in situ* to prevent allergic reactions to tick bites (van Nunen, 2018). Treatment of mammalian meat anaphylaxis is non-specific and the same for any patient with anaphylaxis. The provision of an epinephrine autoinjector, instruction in its use and an anaphylaxis action plan are essential (van Nunen & Ratchford, 2021).

See section on ‘Mammalian meat allergy (MMA) after tick bite’ for more detail on MMA.

Various forms of tick toxicosis affect humans and other animals and in their most severe form result in paralysis of the infested host (Hall-Mendelin et al., 2011). Tick paralysis is a potentially fatal illness of importance to both human and veterinary medicine. In Australia, tick paralysis is largely attributable to holocyclotoxin from *I. holocyclus*, although other species of ticks globally are capable of inducing paralysis (Hall-Mendelin et al., 2011).

To cause host paralysis, a tick must be attached to its host for four to five days (Hall-Mendelin et al., 2011; Hall-Medelin et al. (2011) in Taylor et al., 2019). Paralysis is induced by a toxin that is transmitted to the host in the saliva of a female *I. holocyclus*, when the tick takes a blood meal (Hall-Mendelin et al., 2011). The toxins produced by *I. holocyclus* inhibit acetylcholine release at the neuromuscular junction (Chand et al., 2016), and tend to cause more severe neurological impairment than the toxins from ticks in North America (Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011).

Paralysis can extend even after the tick has been removed (Dehhaghi et al., 2019; Grattan-Smith et al. (1997) in Graves & Stenos, 2017). The progress of paralysis continues for 24 to 48 hours after removal of *I. holocyclus*, in contrast to the short duration seen with North American ticks (Dehhaghi et al., 2019). **It is crucial to carefully observe an affected patient during this period. If the affected patient's condition worsens during this period seek medical attention quickly**. There has not been a death from tick paralysis in Australia since 1945, but it **can be fatal in humans if left untreated.**

Tick paralysis is rare in humans, as a tick must be attached for several (four to five) days to inject enough toxin (Australasian Society of Clinical Immunology and Allergy, 2019b). Tick paralysis, while rare, is usually seen in children rather than adults (Australian Government Department of Health, 2015).

The most commonly affected group is children one to five years of age (Grattan Smith et al. (1997) in Dehhaghi et al., 2019; Grattan-Smith et al. (1997), and Inokuma et al. (2003) in Hall-Mendelin et al., 2011). Doggett noted that occasional cases of tick paralysis do still occur, mainly in children, with these rare cases often unrecognised or misdiagnosed (Doggett, 2004). Guillain-Barré syndrome (GBS) may be commonly confused with tick paralysis (Hall-Mendelin et al., 2011).

Early symptoms of tick paralysis may include:

- rashes, headache, fever, influenza-like symptoms, tenderness of lymph nodes, unsteady gait, intolerance to bright light, increasing weakness of the limbs, and partial facial paralysis (Australian Government Department of Health, 2015; Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011)
- loss of appetite and slurred speech (Grattan-Smith et al. (1997), and Edlow & McGillicuddy (2008) in Hall-Mendelin et al., 2011)
- children becoming subdued, refusing food, and sleeping for excessive periods (Grattan Smith et al. (1997) in Dehhaghi et al., 2019)
- difficulty in reading due to double vision [as a result of eye muscle weakness], nystagmus (repetitive uncontrollable eye movements), or photophobia in older children and adults (Sutherland & Tibballs (2001), and Barker & Walker (2014) in Dehhaghi et al., 2019)
- laboured breathing (Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011).

Over 24 hours the paralysis will continue to involve the arms and the muscles involved in swallowing (Doggett, 2004).

Tick paralysis caused by the Australian paralysis tick (*I. holocyclus*), while rarely severe, can be fatal (Hall-Mendelin et al., 2011). In Australia, between 1914 and 1942, 20 human fatalities were attributed to tick bite, with all but three fatalities being children (Murray & Koch (1969) in Hall-Mendelin et al., 2011), with about 70% of these fatalities being in children under four years of age (Sutherland & Tibballs (2001) in Doggett, 2004). In Australia, there have not been human deaths due to tick paralysis for many decades (since 1945) (Dehhaghi et al., 2019; Doggett, 2004; Grattan-Smith et al. (1997) in Graves & Stenos, 2017; Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011; Barker & Walker (2014) in Taylor et al., 2019). Deaths from the bite of *I. holocyclus* are now rare due to the addition of intensive care-units in regional hospitals and expert medical treatment [advances in intensive care treatment] (Barker & Barker, 2018), and an antivenene.

Untreated tick paralysis can be fatal in humans (Hall-Mendelin et al., 2011). Hall-Mendelin noted the following regarding treatment of tick paralysis:

- Locating and removing all ticks from the patient's body is an important part of therapy, despite the risk of a short-term worsening in the patient's symptoms (Edlow & McGillicuddy (2008) in Hall-Mendelin et al., 2011).
- While ticks are found most commonly on the scalp and behind the ear, a thorough investigation of the patient's body may be warranted.
- While tick antitoxin is available, the heterologous nature of the antiserum can induce serum sickness and anaphylactic shock in humans (Stone et al. (1982) in Hall-Mendelin et al., 2011).
- Progression of paralysis may require mechanical respiratory ventilation in an intensive care unit (Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011).
- The [possible] administration of antibiotics to protect against *Rickettsia* and *Orientia* (Inokuma et al. (2003) in Hall-Mendelin et al., 2011).

A full recovery is usually slow and may take several weeks (Doggett, 2004).

See section on 'Tick-associated toxicosis and paralysis' for more detail.

Impact of tick saliva on the host immune response

Tick saliva is a venom containing hundreds of functionally versatile proteins, injected through a bite and secreted in varying amounts throughout the feeding process (Cabezas-Cruz & Valdés (2014) in Taylor et al., 2019). Ticks, like vampire bats, secrete saliva proteins that have anaesthetic, anticoagulant, vasodilatory, anti-inflammatory and immunosuppressant properties designed to avoid host detection and optimise blood pool-feeding (Šimo et al., 2017; Cabezas-Cruz & Valdés (2014) in Taylor et al., 2019). The venom of ticks, like bees, wasps and scorpions, can cause local or systemic allergic reactions and/or paralysis (Cabezas-Cruz & Valdés (2014) in Taylor et al., 2019).

Tick saliva affects the host immune response in several ways:

- Ticks produce salivary components that degrade bradykinin and sequester histamine to mitigate itch and pain (Šimo et al., 2017).
- Tick saliva strongly suppresses recruitment of blood-borne innate immune cells and notably neutrophils (Šimo et al., 2017).
- Tick saliva quells inflammation at the bite location by diminishing or enhancing secretion of pro- and anti- inflammatory cytokines, respectively (Šimo et al., 2017).
- Tick saliva restricts wound healing and angiogenesis (Francischetti (2010), and Hajnicka et al. (2011) in Šimo et al., 2017). Hard tick[2] salivary molecules are able to bind to the transforming growth factor (TGF)-β1, the platelet-derived growth factor (PDGF), the fibroblast growth factor (FGF)-2, and the hepatocyte growth factor (HGF) depending on the tick species (Hajnicka et al. (2011), and Slovak et al. (2014) in Šimo et al., 2017)
- Tick saliva inhibits the alternative pathway in the host's complement system (Šimo et al., 2017).
- Tick saliva is able to supress the initiation of adaptive immunity by interfering with the capacity of macrophages and dendritic cells to present antigen to T cells and prime appropriate Th responses (Cavassani et al. (2005), Mejri & Brossward (2007), Oliveira et al. (2008), Skallova et al. (2008), and Carvalho-Costa et al. (2015) in Šimo et al., 2017). Ticks promote a Th2 predominant milieu in the host (Ferreira et al. (1999) in van Nunen, 2018).

However, only a minority of the salivary proteins have been functionally annotated, and of these, the putative function has been verified for fewer than 5% (Francisshetti et al. (2009) in Šimo et al., 2017).

With the discovery of MMA, it is now recognised that, in addition to allergic reactions being directed against proteins in tick saliva; when it is injected into humans during bites from some species of ticks, tick saliva can induce an allergy against the alpha-gal carbohydrate molecule. Alpha-gal is a sugar molecule, and is a constituent of the connective tissue of all mammals apart from humans, great apes and Old World monkeys (Galili et al. (1987), Galili et al. (1988), and Galili et al. (2004) in van Nunen, 2018; van Nunen & Ratchford, 2021) and is therefore present in all mammalian meat (and mammalian products) eaten by humans (van Nunen, 2018). The alpha-gal molecule has been identified in the saliva of certain

[2] Hard ticks have a hard flat body and elongated mouthparts with rows of backward pointing teeth. This group includes the most important species that bite humans. See Guidance Note *Introduction to ticks, Australian ticks and tick-borne diseases and illnesses* for more detail.

species of ticks (Centers for Disease Control and Prevention, 2020; Fischer et al. (2020) in van Nunen & Ratchford, 2021).

The saliva of the Australian paralysis tick (*I. holocyclus*) is the most toxic of all tick saliva globally (Sutherland & Tibballs (2001) in Barker & Barker, 2018). It is capable of inducing allergic reactions, including fatal anaphylaxis, paralysis, and death (Australian Government Department of Health, 2015; Brown & Hamilton (1998) in Graves & Stenos, 2017; Taylor et al., 2019; van Nunen, 2015, 2018), although allergic reactions from the bite of *I. holocyclus* are now considered far more common in humans than paralysis (Rappo et al. (2013), and van Nunen (2018) in Sukkanon et al., 2019). Tick-related allergies are the reason many people present to hospital (ED in regions where ticks are hyperendemic (van Nunen & Ratchford, 2021). A two-year survey of a New South Wales hospital ED found over 550 presentations of tick bite, with 34 tick bites resulting in anaphylaxis and over 75% of these requiring adrenaline use (Rappo et al., 2013). Tick anaphylaxis was responsible for four deaths in Australia between 1997 and 2013 (Mullins et al. (2016), and McGain et al. (2016) in van Nunen & Ratchford, 2021).

Australian Parliamentary Inquiry into allergy and anaphylaxis

In 2020, the House of Representatives Standing Committee on Health, Aged Care and Sport (the Committee) published its report *Walking the allergy tightrope,* following the Parliamentary Inquiry into allergies and anaphylaxis undertaken in 2019. This report considered the evidence provided in submissions regarding tick allergy.

The Committee reported that TiARA had advised that, as of 2019, tick-induced allergies comprise of:

- mammalian meat allergy (MMA)
- tick anaphylaxis
- food carbohydrate-induced enterocolitis syndrome (FCIES)
- large local reactions (Tick-induced Allergies and Awareness (TiARA), Submission 137 in Parliament of Australia, 2020; Tick-induced Allergies Research and Awareness, 2019).

TiARA noted in its submission to the Inquiry that FCIES was an additional novel entity only described in 2019 (Tick-induced Allergies Research and Awareness, 2019). The limited available information about FCIES is included in the 'MMA' section of this Guidance Note.

Additional to the list of tick-induced allergies reported by the Committee, is MMA in individuals with the co-existing condition of mastocytosis. TiARA highlighted this condition in its educational resources (Tick-induced Allergies Research and Awareness, n.d.-b). Available information on this condition can be found under the 'MMA' section within this Guidance Note.

The Committee reported the following findings on tick allergy from the submissions received:

- The connection between tick allergy and anaphylaxis is a relatively new discovery and is the only allergy where the trigger (tick bite) is known. MMA after tick bite was first reported in 2007 in Australia by Dr Sheryl van Nunen et al. MMA has been identified in 17 countries[3] around the world (Tick-induced Allergies Research and Awareness (TiARA), Submission 137 in Parliament of Australia, 2020).
- The allergen in mammalian meat was found to be a carbohydrate molecule called galactose-alpha, 1,3-galactose ("alpha gal"). In contrast, tick anaphylaxis, is due to the development of an antibody to tick salivary protein (TiARA Submission 137 in Parliament of Australia, 2020).
- Worldwide, Australia has the highest prevalence of MMA and TA. The prevalence rate for MMA is 113 out of 100,000. TiARA commented that 'modelling the effects of global warming indicates that higher tick exposure will occur in the future' (TiARA Submission 137 in Parliament of Australia, 2020).
- More than 50% of Australians live in regions where the Australian paralysis tick is endemic and a second tick species in Western Australia has been described as a cause of MMA, increasing the exposure of the Australian population to around 60% (TiARA Submission 137 in Parliament of Australia, 2020).
- TiARA stated that tick anaphylaxis has caused four fatalities between 1997 and 2013 (TiARA Submission 137 in Parliament of Australia, 2020).

[3] Dr Sheryl van Nunen advised MMA is currently reported in over 26 other countries, as at June 2022.

Confirming an allergy to ticks

ASCIA provides the following advice regarding confirming an allergy to ticks (Australasian Society of Clinical Immunology and Allergy, 2019b):

- Tick allergy should be confirmed by a clinical immunology/allergy specialist, noting there is a link between tick allergy and the development of allergic reactions to mammalian meats and/or mammalian meat-derived gelatine (Australasian Society of Clinical Immunology and Allergy, 2019b).
- At this time, there is no reliable skin test or blood test for allergen specific IgE antibodies to confirm a diagnosis of tick allergy. Australian researchers have identified that the allergens that cause problems are proteins in tick saliva (Broady (2013) in van Nunen, 2018). Diagnosis is currently based on the history of the reaction.
- Researchers have identified that the following blood allergy tests are positive in the majority of people with serious allergic reactions to tick bites [tick anaphylaxis]. The following blood tests for allergen specific IgE may assist in confirming a diagnosis:
    - Mammalian meats Immunocap.
    - Alpha-galactose Immunocap. Alpha-galactose is a sugar molecule present in meat from mammals other than humans, great apes and Old World monkeys. It is also found in the gut of ticks.
    - Blood tests for mast cell tryptase may also be useful. Tryptase is an enzyme that is increased in people with a condition called [systemic] mastocytosis. It is associated with a higher risk of allergic reactions to many allergic triggers including insect stings and tick bites. People with higher tryptase levels may have more severe anaphylactic reactions to insect tings and bites (Australasian Society of Clinical Immunology and Allergy, 2019b).

More recently, in 2021, van Nunen & Ratchford included a diagnostic pathway for ‘Diagnosis and management of MMA’ in their article ‘Managing mammalian meat allergy and tick anaphylaxis’ (van Nunen & Ratchford, 2021).

Severe allergic reactions to tick bites

Severe allergic reactions, including tick anaphylaxis, are a potentially life threatening severe allergic reaction that require immediate treatment with adrenaline (epinephrine). Anaphylaxis is a medical emergency Call an ambulance (000 in Australia), immediately after giving an adrenaline autoinjector (EpiPen®, Anapen®). See section on 'First aid for anaphylaxis, including tick anaphylaxis' for more detail.

Mammalian meat allergy (MMA) after tick bites and tick anaphylaxis are the most serious tick-induced allergies; they are often severe and should be largely avoidable (van Nunen, 2018). MMA is due to an IgE-mediated reaction to an allergen, a carbohydrate moiety, α-gal or alpha-gal (galactose-α-1,3-galactose) in mammalian meat (Tick-induced Allergies Research and Awareness, 2019; Commins et al. (2009) in van Nunen, 2018). However, the allergic reaction in MMA after tick bites is in contrast to tick anaphylaxis, which is due to the development of allergy antibody to tick salivary protein (Tick-induced Allergies Research and Awareness, 2019). While each of these reaction types relies on IgE mediation, tick anaphylaxis and MMA present quite differently clinically.

Anaphylaxis caused by tick bites

Severe allergic reactions (anaphylaxis) to the Australian paralysis tick (*I. holocyclus*) have been reported (Australasian Society of Clinical Immunology and Allergy, 2019b; Tick-induced Allergies Research and Awareness, n.d.-b), with tick anaphylaxis first described in Australia in 1940 (McKay (1940) in Taylor et al., 2019; McKay (1940) in van Nunen, 2018). Subsequent reports of tick anaphylaxis in Australia are described in the section on 'Incidence of tick anaphylaxis'.

Anaphylaxis, including tick anaphylaxis, is a potentially life threatening severe allergic reaction, that requires immediate treatment with adrenaline (epinephrine). Anaphylaxis should always be treated as a medical emergency (Australasian Society of Clinical Immunology and Allergy, 2021b). While the severity of the anaphylactic reaction can range from Mueller grade I to IV, Australian research found 74% of reactions in tick anaphylaxis to be grade IV (van Nunen et al. (2014) in Taylor et al., 2019), the most severe grade of reaction.

Information on 'Signs and symptoms of allergic reaction', 'EpiPen® administration', and 'Anapen® administration', by A&AA, is available at https://allergyfacts.org.au/resources/videos-from-a-aa.

Life-threatening allergic reactions to ticks are much more common than similarly severe reactions to bees or wasps (Tick-induced Allergies Research and Awareness, n.d.-b) [in regions where tick bites are common].

Anaphylaxis occurs when the tick is disturbed, as this may cause the tick to inject more allergen-containing saliva (Australasian Society of Clinical Immunology and Allergy, 2019b; Tick-induced Allergies Research and Awareness, n.d.-b). Australian researchers have identified the allergens responsible for tick anaphylaxis as proteins in the tick saliva (Tick-induced Allergies Research and Awareness, n.d.-b). Tick anaphylaxis is a classic immediate

IgE-mediated allergic reaction to one of five tick salivary proteins that is injected into the host by the tick during feeding (Gauci et al. (1988), Gauci et al. (1989), Gauci et al. (1998), Broady (2013), Dorey (1998), and Padula (2008) in van Nunen, 2018; Gauci et al. (1988), Gauci et al. (1989), Gauci et al. (1998), Broady (2013), Dorey (1998), and Padula (2008) in van Nunen & Ratchford, 2021). Bites from larval and nymph ticks may prime the production of allergen specific IgE to tick salivary proteins, however, it is only the bite of an adult tick that can trigger an episode of anaphylaxis, which occurs when the tick is disturbed by inappropriate handling (Stone (2000) in van Nunen & Ratchford, 2021).

Anaphylactic reactions to tick bites have been fatal, though fatalities are rare (Tick-induced Allergies Research and Awareness, n.d.-b). Four deaths due to tick anaphylaxis have occurred in Australia between 1979 and 2013 (McGain et al. (2016), and Mullins et al. (2016) in van Nunen, 2018; McGain et al. (2016), and Mullins et al. (2016) in van Nunen & Ratchford, 2021). These four recorded human fatalities from tick anaphylaxis all occurred shortly after removal of a live adult tick and despite resuscitation with adrenaline (McGain et al., 2016; McGain et al. (2016) in Taylor et al., 2019). While three of the fatalities occurred in people with known tick allergies, one had not previously reacted to a tick bite, prompting Taylor et al. to caution that given the potential for severe reaction and the inability to predict severity based on previous reactions, every tick bite should be managed with care (Taylor et al., 2019).

Worldwide, tick anaphylaxis occurs most commonly in Australia, and is becoming increasingly prevalent [here] (van Nunen (2015), van Nunen (2014), and Rappo et al. (2013) in van Nunen, 2018).

Anaphylaxis, including tick anaphylaxis

Anaphylaxis is defined by the Australian Government Department of Health as the most severe form of allergic reaction and is life threatening if not immediately treated. Anaphylaxis involves more than one body system, for example: skin, respiratory, gastrointestinal and/or cardiovascular (Department of Health website, Reporting and managing adverse vaccination events in Parliament of Australia, 2020). The most common triggers of anaphylaxis are noted to be foods, insect stings, and drugs or medications (Parliament of Australia, 2020).

The ASCIA Guidelines for acute management of anaphylaxis (Australasian Society of Clinical Immunology and Allergy, 2021a) describes two presentations in their definition of anaphylaxis:

- Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema), plus involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms.
- Any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present (Australasian Society of Clinical Immunology and Allergy, 2021a).

See section on ‘ASCIA Guidelines Acute Management Anaphylaxis 2021’.

When tick anaphylaxis occurs, the treatment is the same as for anaphylaxis to any agent (Tick-induced Allergies Research and Awareness, n.d.-b; van Nunen, 2018; van Nunen & Ratchford, 2021).

Incidence of tick anaphylaxis

In Australia, the true incidence of anaphylaxis from any cause is unknown, as Australia lacks a structured reporting system to capture data on the incidence of anaphylaxis (Parliament of Australia, 2020).

Within Australia, anaphylaxis to hard ticks was first reported in the Medical Journal of Australia in 1940 (McKay (1940) in van Nunen, 2018).

Subsequent reports of tick anaphylaxis in Australia were published in:

- the 1960s (Trinca (1964) and Banfield (1966) in van Nunen, 2018)
- the 1980s (Gauci et al. (1989) in Tick-induced Allergies Research and Awareness, 2019; Kemp (1986) in van Nunen, 2018)
- 1998 (Brown & Hamilton (1998) in van Nunen, 2018)
- 2013 (Rappo et al., 2013; Rappo et al. (2013) in van Nunen, 2018)
- 2019 (Taylor et al., 2019).

TiARA's 2019 submission to the Parliamentary Inquiry into allergies and anaphylaxis demonstrated not only the incidence trajectory of tick anaphylaxis cases over time, both in Australia and overseas, but the higher incidence of tick anaphylaxis in Australia (Tick-induced Allergies Research and Awareness, 2019):

> *1940 McKay, Australia (one case)*
> *1964 Trinca, Australia, (one case)*
> *1966 Banfield, Australia (one case)*
> *1985 Kemp, Australia (one case)*
> *1988-1989 Gauci et al., Australia (12 cases)*
> *1991, 1991 van Wye, US (one case described twice)*
> *1998 Moneret-Vautrin et al., France (one case)*
> *2001 Fernandez et al., Spain (two cases)*
> *2003 Acero et al., Spain (one case)*
> *2007 Valls et al., Spain (one case)*
> *2013 Rappo et al., Australia (34 cases)*
> *2017 Mateos-Hernández et al., Spain (two cases) (Tick-induced Allergies Research and Awareness, 2019).*

The most recent studies on tick anaphylaxis, by Rappo and colleagues (Rappo et al., 2013) and Taylor and colleagues (Taylor et al., 2019) were undertaken at Mona Vale Hospital in Sydney, New South Wales. These studies are described below.

Rappo et al. (2013) study

Rappo et al. undertook a retrospective analysis of patients presenting with tick bite at the ED at Mona Vale Hospital (MVH ED) on Sydney's Northern Beaches over a two-year period between 1 January 2007 and 1 January 2009. In this study 37% of patients (211 out of 566) were documented as having an allergic reaction to a tick, of which 6% (34 out of 566) were cases of anaphylaxis (Rappo et al., 2013).

In Rappo et al.'s study, anaphylaxis was defined as the presence of cardiovascular and/or respiratory signs and symptoms, and the involvement of another organ system, such as skin or gastrointestinal tract. In 76% (26 out of 34) of the anaphylaxis cases the tick had been killed or removed prior to presentation at the ED; and the remaining eight cases had developed anaphylaxis prior to removal of the tick in hospital. Of the 34 patients who were

documented as cases of anaphylaxis, 40% (13 out of 34) had a history of allergy or previous episode of anaphylaxis, whereas only 4% (20 out of 532) that did not develop anaphylaxis from the tick bite had a previous anaphylaxis (Rappo et al., 2013). Rappo et al. commented that their data reflects data published by Gauci et al. in 1989, suggesting an association between tick anaphylaxis and atopy (Gauci et al. (1999) in Rappo et al., 2013). As such, Rappo et al. advised that patients with a history of anaphylaxis:

- should avoid tick-infested areas and contact with ticks (Rappo et al., 2013), advice that is promulgated by Australian authorities and medical professional organisations (Australasian Society of Clinical Immunology and Allergy, 2019b; Australian Government Department of Health, 2015; Tick-induced Allergies Research and Awareness, n.d.-b)
- who present with a history of tick bite should be monitored closely for signs and symptoms of anaphylaxis (Rappo et al., 2013).

Taylor et al. (2019) study

Taylor et al.'s study over a six-month period during the peak tick season in 2016 at the MVH ED in Sydney (New South Wales) was aimed at investigating killing ticks *in situ* to prevent allergic and anaphylactic reactions in humans. The study provided data on the incidence of tick presentations and allergic/anaphylactic reactions. The authors noted that the ED saw an average of 20 tick bite presentations per month and more than 50 per month during peak tick season. Taylor et al. used the 2017 ASCIA criteria for anaphylaxis (Australasian Society of Clinical Immunology and Allergy. Acute management of anaphylaxis (2017) in Taylor et al., 2019). Allergic reaction was defined as typical skin features as listed in ASCIA criteria (urticaria, erythema/flushing, and/or angioedema), occurring distant from the bite site, therefore excluding small and large local reactions (Taylor et al., 2019).

Of the 121 patients who presented to the ED for tick bites and were included in the study, 61 patients had ticks killed with Wart-Off Freeze® or Lyclear® Scabies Cream before removal with fine-tipped forceps or a Tick Twister® tool. Of these 61 patients, 28 were known to be tick-hypersensitive. Three (5%) of these 61 patients, two of whom were known to be tick-hypersensitive, had allergic reactions, none of which were anaphylactic. The other 50 patients presented to the ED having already removed ticks by various methods. Of these 50 patients, 86% (43 out of 50) experienced allergic reactions, two of which were anaphylactic and 41 were allergic reactions. In the two patients who had anaphylactic reactions, anaphylaxis occurred shortly after removal of the tick and before presentation to ED. Both patients were successfully treated with adrenaline. The anaphylactic reactions were both in patients who self-removed live ticks - one with fingers and the other with tweezers; neither patient had previously had an allergic reaction to a tick bite.

Ten allergic reactions occurred in the 71 patients who presented to ED with ticks *in situ*. Five patients suffered allergic reactions before presentation at the ED, despite no attempt at tick removal, but the authors noted the ticks had likely been disturbed by some other method. The other five patients had live ticks removed in the ED. Three of these patients refused tick killing and had no reaction when the tick was removed using fine-tipped forceps despite one patient having known hypersensitivity. Two patients had ticks on eyelids contraindicating killing, one of whom had known hypersensitivity; both patients had allergic reactions post removal (Taylor et al., 2019).

Taylor et al. noted that compared with the previous study at the same hospital (by Rappo et al. 2013 described above), the number of tick bite presentations remained stable at about 290 each year, as did the percentage of these that had allergic reactions (about 36%), but anaphylaxis reactions were far fewer. Between 2007 and 2009 they noted 34 cases of anaphylaxis had been identified in Rappo et al.'s 2013 study, and in their study there were only two cases (Taylor et al., 2019). Taylor et al. commented that hypersensitivity requires previous exposure, and although severity varies slightly unpredictably, it is thought to increase with each bite. Therefore, in their view, one possible explanation was improved public awareness at an earlier stage of hypersensitivity through local campaigns and publications in local and national media. They noted that 89% of known hypersensitive patients in their study either presented to ED for management or used Wart-Off Freeze® or Lyclear® at home and only 7.1% had allergic reactions after approved methods for management of tick bites were used (Taylor et al., 2019).

Internationally documented cases of tick anaphylaxis have been reported in the literature since 1991 (van Nunen, 2018). Cases have been reported in:

- the US (van Wye, Hsu, Lane et al. (1991), and van Wye, Hsu, Terr et al. (1991) in van Nunen, 2018) [the two papers were based on one patient]
- France (Moneret-Vautrin (1998) in van Nunen, 2018) [one patient]
- Spain (Fernández-Soto et al. (2001), Acero et al. (2003), Valls et al. (2007), Mateos-Hernández et al. (2017) in van Nunen, 2018) [number of cases not provided][4]
- Japan (Kaneko et al., 2019) [12 patients; tick species not noted].

Ticks that cause anaphylaxis

Globally, the following tick species have been identified as causative of tick anaphylaxis (van Nunen, 2018):

- *I. holocyclus* (Australian paralysis tick) (Rappo et al. (2013) in van Nunen, 2018)
- *Ixodes pacificus* (western-black-legged tick) (van Wye, Hsu, Lane et al. (1991) in van Nunen, 2018)
- *Ixodes ricinus* (castor bean tick) (Moneret-Vautrin et al. (1998), and Fernández et al. (2001) in van Nunen, 2018)
- *Rhipicephalus bursa* (Anatolian brown tick) (Acero et al. (2003), and Mateos-Hernández et al. (2017) in van Nunen, 2018)
- *Rhipicephalus sanguineus* (brown dog tick, kennel tick or pantropical dog tick) (Valls et al. (2007) in van Nunen, 2018)
- *Hyalomma marginatum* (Mediterranean Hyalomma) (Mateos-Hernández et al. (2017) in van Nunen, 2018).

[4] While the number of cases was not provided by the author, according to the information from TiARA provided earlier in this section, the number of cases of tick anaphylaxis reported for Spain was six.

Symptoms of tick anaphylaxis in the general population

Symptoms of a severe allergic reaction (anaphylaxis) include any acute onset illness which evolves rapidly over minutes immediately after removing only an adult tick. Symptoms include skin reactions such as welts or swellings, difficulty breathing, closing over of the throat, tongue swelling, impending loss of consciousness (faintness), sense of impending doom, or loss of consciousness. TiARA notes that, crucially, people who have an anaphylactic reaction to a tick bite react **only when the tick is disturbed** (Tick-induced Allergies Research and Awareness, n.d.-b).

For information by A&AA on 'Signs and symptoms of allergic reaction', 'EpiPen® administration', and 'Anapen® administration', go to https://allergyfacts.org.au/resources/videos-from-a-aa.

Collective advice from TiARA and ASCIA notes that the symptoms of anaphylaxis, including tick anaphylaxis, are **one or more** of the following, and starting within seconds to a few minutes of forcibly removing a tick, for example with household tweezers:

- Generalised itch
- Hives or welts may appear
- Swelling of lips, face, eyes or tongue
- Swelling/tightness in the throat or a sensation of throat closure
- Difficulty talking and/or hoarse voice
- A feeling of 'impending doom'
- Generalised feeling of warmth
- Tingling mouth
- Difficult/noisy breathing and/or persistent cough (unlike the cough in asthma, the onset of coughing during anaphylaxis is usually sudden)
- Abdominal pain, vomiting
- Persistent dizziness or collapse
- Pale and floppy (young children) (Australasian Society of Clinical Immunology and Allergy, 2021a; Tick-induced Allergies Research and Awareness, n.d.-b).

In Rappo et al.'s study of 566 patients presenting with tick bite at an Australian hospital ED, described above, conjunctival tearing and erythema were the most common symptoms at presentation to the ED, affecting over 38% of cases (220 out of 566), while itch and urticaria were present in 19% (107 out of 566) of cases at presentation (Rappo et al., 2013). The least common symptoms at presentation were angioedema, wheeze, shortness of breath and hypotension. Rappo et al. reported that of the 566 patients overall, angioedema was present in 6% (36 out of 566) of patients at presentation, whereas 4% (24 out of 566) of patients presented with periorbital angioedema. Wheeze and shortness of breath was present in 4% (24 out of 566) of patients, and 4% (20 out of 566) of patients presented with throat tightness. One percent (8 out of 566) of patients were hypotensive at presentation (systolic pressure < 90mmHg).

The symptoms of the 34 recorded cases of anaphylaxis were reported:

- Ninety-four per cent (32 out of 34) had cutaneous features including urticaria, erythema, conjunctival tearing and angioedema
- Fifty-nine per cent (20 out of 34) had dyspnoea, wheeze or throat tightness

- Forty-one per cent (14 out of 34) had angioedema
- Twenty-six per cent (9 out of 34) had tachycardia and/or hypotension
- Seventeen per cent (6 out of 34) had nausea or vomiting (Rappo et al., 2013).

While Rappo et al. noted that although cutaneous symptoms were the most common feature in patients documented as having anaphylaxis, three cases had no cutaneous symptoms. The authors commented this finding highlights the importance of a thorough clinical examination and the recognition that tick bite-induced anaphylaxis can occur in the absence of cutaneous symptoms (Lockey et al. (1988) in Rappo et al., 2013), as with other allergens. This finding of an absence of cutaneous symptoms in patients with tick anaphylaxis in Rappo et al.'s Australian study is concordant with ASCIA's second definition of anaphylaxis (see section on 'Anaphylaxis, including tick anaphylaxis' above) that notes typical skin features may not be present in anaphylaxis (Australasian Society of Clinical Immunology and Allergy, 2021a).

Symptoms of anaphylaxis in pregnancy

The 2020 ASCIA Guidelines *Acute management of anaphylaxis in pregnancy* notes that the signs and symptoms of anaphylaxis [in general, and therefore are applicable to tick anaphylaxis] in pregnant women are the same as for non-pregnant women, although several additional features are possible. Additional signs and symptoms include (Hepner et al. (2013), and Simons and Schatz (2013) in Australasian Society of Clinical Immunology and Allergy, 2020):

- persistent hypotension - may be the predominant feature
- intense vulvar and vaginal itching (particularly if allergic reaction/IgE-mediated reaction to latex)
- low back pain
- uterine cramps
- foetal distress.

Of relevance to ticks, under signs and symptoms of maternal anaphylaxis, ASCIA advises anaphylaxis to foods and **insect venom** should also be considered (Simons & Schatz (2012), and McCall et al. (2018) in Australasian Society of Clinical Immunology and Allergy, 2020).

For information by A&AA on 'Signs and symptoms of allergic reaction', 'EpiPen® administration', and Anapen® administration', go to https://allergyfacts.org.au/resources/videos-from-a-aa.

Clinical and other features of tick anaphylaxis

The severity of reaction in tick anaphylaxis can range from Mueller grade I to IV; with one Australian study finding 74% of reactions to be grade IV, which is the most severe grade (van Nunen et al. (2014) in Taylor et al., 2019).

Van Nunen has described the clinical and other features of tick anaphylaxis in two publications (van Nunen, 2015, 2018). In her 2018 paper, van Nunen reported the following clinical features of tick anaphylaxis (van Nunen, 2018):

- Tick anaphylaxis is only seen with bites from adult ticks
  (van Nunen (2015), van Nunen (2014), Rappo et al. (2013), Gauci et al. (1988), Broady

(2013), Dorey (1998), Padula (2008), Commins & Plats-Mills (2011), Kemp (1986), Brown & Hamilton (1998), and van Nunen (2014) in van Nunen, 2018)

- Tick anaphylaxis is becoming more commonly seen in tick-endemic areas of Australia (van Nunen (2015), van Nunen (2014), Rappo et al. (2013), Gauci et al. (1989), McKay (1940), Trinca (1964), Banfield (1966), Kemp (1986), and Brown & Hamilton (1998) in van Nunen, 2018)
- Tick anaphylaxis is uncommon in countries other than Australia (van Wye, Hsu, Lane et al. (1991), van Wye, Hsu, Terr et al. (1991), Moneret-Vautrin et al. (1998), Fernández et al. (2001), Fischer et al. (2016), Acero et al. (2003), Valls et al. (2007), and Mateos-Hernández et al. (2017) in van Nunen, 2018). The two papers by van Wye et al. (1991) are based on one patient)
- Tick anaphylaxis is usually severe (>74% Mueller grade III or IV) (Gauci et al. (1989), McKay (1940), Trinca (1964), Banfield (1966), Kemp (1986), Brown & Hamilton (1998), Sánchez et al. (2014), and van Nunen et al. (2014) in van Nunen, 2018)
- Tick anaphylaxis is more likely to occur in older individuals (>50%, >50 years of age) (van Nunen et al. (2014) in van Nunen, 2018)
- Tick anaphylaxis may be fatal (four lethal reactions in Australia) (McGain et al. (2016), and Mullins et al. (2016) in van Nunen, 2018)
- Tick anaphylaxis may be provoked when the tick is disturbed or removed inappropriately (van Nunen (2015), van Nunen (2014), Gauci et al. (1989), and van Nunen et al. (2014) in van Nunen, 2018)
- Tick anaphylaxis is very unlikely to occur when the tick is killed *in situ* (Taylor et al., 2019; van Nunen et al. (2014) in van Nunen, 2018).

Fatalities from tick anaphylaxis

Four fatalities from tick bite anaphylaxis have occurred in Australia (McGain et al. (2016), and Mullins et al. (2016) in van Nunen, 2018). Two recent studies have investigated these fatalities from tick-bite related anaphylaxis (McGain et al., 2016; Mullins et al., 2016). Mullins et al.'s study identified numbers of anaphylaxis fatalities, including insect sting/tick-related anaphylaxis fatalities over time and examined characteristics of fatalities. McGain et al. also identified numbers of tick anaphylaxis fatalities over time but also described the cases. These studies are described below.

Mullins et al. (2016) study

Mullins et al.'s study of anaphylaxis fatalities in Australia from 1997 to 2013 used data from the Australian Bureau of Statistics (ABS) 1997-2013 and the National Coronial Investigation System (NCIS) 2000-2013 and was aimed at determining whether Australian anaphylaxis fatalities were increasing in parallel with other countries (Mullins et al., 2016). The NCIS data was used to examine characteristics of recorded fatalities. The ABS data recorded 324 anaphylaxis fatalities by cause, of which 41 were attributed to insect stings/bites. The ABS data was not broken down further into anaphylaxis fatalities by tick bites. Mullins et al. reported that of all 41 cases of anaphylaxis fatality by insect sting/bite, all occurred in individuals aged 15 years and over (Mullins et al., 2016). In the NCIS database, a total of 147 verified NCIS deaths were examined in detail. Of the insect/sting/tick bite fatalities, 91% (30 out of 33) were male with a median age of 50 years (IQR: 41 to 56; range: 19 to 79 years). Of the 33 insect sting/tick bite deaths, tick bites accounted for three fatalities; the same number of anaphylaxis fatalities recorded for ant stings (n=3). Anaphylaxis fatalities from tick

bites were higher than for wasps (n=2) or unspecified sting (n=1), but much lower than for honeybees (n=24). Mullins et al. noted the three tick bite fatalities occurred within minutes of deliberate manual attempts at tick removal (Mullins et al., 2016).

McGain et al. (2016) study

McGain and colleagues identified four fatalities between 1 January 1979 and 31 December 2013, where a coronial cause of death certificate attributed death due to anaphylaxis after a tick bite. One record from 1979 to 2000 was obtained from the ABS Mortality Data Set and a hospital patient file record. All fatalities were in adults below the age of 50 years; three were males, one was female. Three of the adults had a history of tick bite allergy; one had no clear history of tick bite allergy. One person lived in Queensland, and three people lived in New South Wales. All cases of fatal anaphylaxis occurred from late winter into summer (August, September, October and February). McGain et al. commented these cases of fatality were most likely attributed to the Australian paralysis tick (*I. holocyclus*) and represented the first documented fatalities from tick bite-related anaphylaxis (McGain et al., 2016).

A brief description of each fatal case is described below. Further detail of treatment provided is described in the clinical communications article by McGain et al. (2016).

Fatality 1: The first fatality was of a male who had a history of severe prior allergy to both ticks and bees, including requiring adrenaline for a reaction to a bee sting and, four and five years later, after tick bites. He was referred to an allergist after the second tick bite. He had been given an adrenaline spray and an epinephrine autoinjector device for delivering 0.3 mg of injectable adrenaline. He had been advised to kill further ticks *in situ* and to consider moving to a nonendemic area. The fatal event began as the man dislodged a small tick from his neck. He rapidly developed a rash, became severely dyspneic, and lost consciousness. The spouse injected adrenaline via the autoinjector. Despite intensive medical intervention by a GP and in hospital, he was pronounced brain dead the day after admission. McGain et al. commented this ‘first case of fatality is one of an apparent failure of an epinephrine autoinjector device to prevent fatal anaphylaxis’; however, McGain et al. noted it was not apparent whether this was due to device or operator failure, delay in administration or an epinephrine-resistant anaphylaxis (Smith et al. (1980), and Bautista et al. (2002) in McGain et al., 2016). The authors also commented this fatality provided the first report of a potential cross-reaction between bee and tick allergens as well as the first instance of disseminated intravascular coagulation complicating tick bite anaphylaxis (McGain et al., 2016).

Fatality 2: The second fatality occurred in a male with a history of pneumothorax and mild asthma. This patient collapsed with difficulty breathing soon after a tick was removed from his posterior scalp. Despite CPR by family and ambulance staff, as well as prehospital adrenaline administration, he could not be revived and was declared dead at a nearby hospital. There was no clear history of prior tick allergy in this man (McGain et al., 2016).

Fatality 3: The third fatality was a man who collapsed and died within an hour of a tick being removed from his hand. The man had been outdoors earlier that day and had difficulty breathing on witnessed tick removal. Despite adrenaline injections and resuscitation by paramedics, he could not be revived. He had a history of severe reaction to a tick bite 12 months previously (McGain et al., 2016).

Fatality 4: The fourth fatality was in a female with a history of tick bite allergy, Takayasu’s arteritis, hypertension, depression, asthma, chronic airways disease, and smoking. She told

her next of kin that she was unwell and discovered a tick at the back of her head, which was allegedly removed. She then collapsed, an ambulance was called, CPR was conducted, and she was conveyed to hospital. At the hospital, a CT scan showed global hypoxic ischemic brain damage, and she could not be resuscitated. The post-mortem revealed a tick in her scalp. McGain et al. noted there was no information available on her prior tick allergy management (McGain et al., 2016).

McGain et al. noted that crucially, these people suffered an anaphylactic reaction to a tick bite only when the tick was disturbed, prompting the reminder for public and patient counselling and first aid for tick-induced anaphylaxis in addition to tick avoidance for primary prevention (McGain et al., 2016). They noted the lack of specific immunotherapy increases the importance of anaphylaxis emergency kits and patient (and family) education for those with life-threatening allergy to tick bites (McGain et al., 2016).

Of relevance to tick paralysis (see section on 'Tick-associated toxicosis and paralysis'), McGain et al. commented that given the lack of recent fatal tick paralysis cases, and the temporal and spatial clustering of these events, tick-induced anaphylaxis seems as important, if not potentially more significant than tick toxicity (McGain et al., 2016).

First aid for tick-induced anaphylaxis

Anaphylaxis is a medical emergency.

Anaphylaxis, including tick anaphylaxis, is a potentially life threatening severe allergic reaction, that requires immediate treatment with adrenaline (epinephrine). Anaphylaxis should always be treated as a medical emergency. Call an ambulance (000 in Australia), immediately after giving an adrenaline autoinjector (EpiPen®, Anapen®) (Australasian Society of Clinical Immunology and Allergy, 2021b).

When an anaphylaxis to a tick occurs, the treatment is the same as for anaphylaxis to any agent (Tick-induced Allergies Research and Awareness, n.d.-b; van Nunen, 2018; van Nunen & Ratchford, 2021).

For information by A&AA on 'Signs and symptoms of allergic reaction', 'EpiPen® administration', and 'Anapen® administration', go to https://allergyfacts.org.au/resources/videos-from-a-aa.

Collective advice from TiARA and ASCIA on first aid and immediate actions for anaphylaxis, including tick anaphylaxis, is as follows (Australasian Society of Clinical Immunology and Allergy, 2019a; Tick-induced Allergies Research and Awareness, n.d.-b):

- Lie the person down if possible and elevate the legs as this maximises blood flow to the head and therefore oxygen to the brain. **Do NOT allow them to stand or walk.**
- **GIVE ADRENALINE INJECTOR.** If there is an adrenaline autoinjector (EpiPen®, Anapen®) available, use it while waiting for emergency services if there is any closing over of the throat, breathing difficulty or impending loss of consciousness.
- Call 000 and explain that the reaction is life-threatening.
- If a person is living alone or is alone and suffering tick-induced anaphylaxis symptoms, s/he should open the front door, chock it open, and then lie down and put their feet up on a chair/lounge. As above, the person who is alone should call 000 and explain that the reaction is life-threatening. They should also use an adrenaline autoinjector (EpiPen®, Anapen®) if available, while waiting for emergency services if there is any closing over of

their throat, breathing difficulty or impending loss of consciousness. The person should leave a note beside them noting they have been bitten by a tick, if time permits.

ASCIA Guidelines for acute management of anaphylaxis, including tick-anaphylaxis

ASCIA has published two guidelines, described below, that are appropriate to acute management of tick anaphylaxis. These guidelines are:

- Acute Management Anaphylaxis (severe anaphylactic reactions) (Australasian Society of Clinical Immunology and Allergy, 2021a)
- Acute Management Anaphylaxis in pregnancy (Australasian Society of Clinical Immunology and Allergy, 2020).

ASCIA Guidelines Acute Management Anaphylaxis 2021

The ASCIA Guidelines *Acute Management Anaphylaxis (severe allergic reactions) 2021* are intended for medical practitioners, nurses and other health professionals who provide first responder emergency care. The Guidelines are available at https://www.allergy.org.au/hp/papers/acute-management-of-anaphylaxis-guidelines (Australasian Society of Clinical Immunology and Allergy, 2021a).

The ASCIA 2021 Guidelines state that the information provided is consistent with the following publications:

- Updated anaphylaxis guidelines: management in infants and children 2021: www.nps.org.au/australian-prescriber/articles/updated-anaphylaxis-guidelines-management-in-infants-and-children
- Anaphylaxis: emergency management for health professionals 2018: www.nps.org.au/australian-prescriber/articles/anaphylaxis-emergency-management-for-health-professionals.

The ASCIA 2021 Guidelines state they are based on the following international guidelines:

- International Liaison Committee on Resuscitation (ILCOR) and Australian and New Zealand Committee on Resuscitation (ANZCOR) guidelines.
- American Academy of Allergy, Asthma and Immunology (AAAAI) Anaphylaxis- a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Analysis: www.jacionline.org/article/S0091-6749(20)30105-6/fulltext.
- World Allergy Organisation (WAO) Anaphylaxis Guidance 2020: www.worldallergyorganizationjournal.org/article/S1939-4551(20)30375-6/fulltext.

The topics covered in the 10 sections and Appendix of the ASCIA Guidelines *Acute Management Anaphylaxis 2021* are listed below. Where ASCIA has highlighted a specific point in red in the guideline, this has been included below in a box under the relevant section heading.

1. Definition and clinical diagnostic criteria for anaphylaxis.
2. Signs and symptoms of allergic reactions.
3. Immediate actions for anaphylaxis.

- **LAY PERSON FLAT – do NOT allow them to stand or walk.**

- **GIVE ADRENALINE INJECTOR – Give intramuscular injection (IMI) adrenaline into outer mid-thigh** without delay using an adrenaline injector if available OR adrenaline ampoule/syringe. **Adrenaline (epinephrine) is the first line treatment for anaphylaxis.**
- **IF IN DOUBT GIVE ADRENALINE.**
- **ALWAYS GIVE ADRENALINE FIRST, then asthma reliever** if someone with known asthma and allergy to food, insects or medication has SUDDEN BREATHING DIFFICULTY (including wheeze, persistent cough or hoarse voice) even if there are no skin symptoms.

4. Anaphylaxis triggers and reaction times.
5. Adrenaline administration and doses.

- **Adrenaline is the first line treatment for anaphylaxis and acts to reduce airway mucosal oedema, induce bronchodilation, induce vasoconstriction and increase strength of cardiac contraction**

6. Management of anaphylaxis in pregnancy and infants.
7. Positioning of patients with anaphylaxis.

- Fatality can occur within minutes if a patient stands, walks or sits suddenly
- Patients must NOT walk or stand, even if they appear to have recovered.

8. Equipment required for acute management of anaphylaxis.
9. Supportive management and additional measures- See Appendix for additional information.
10. Actions after administration of adrenaline.

Appendix: Acute management of anaphylaxis. This additional information is intended for health professionals working in emergency departments, ambulance services, and rural or regional areas, who provide emergency care.

ASCIA Guidelines Acute management of anaphylaxis in pregnancy 2020

ASCIA advises there are limited studies exploring the management of patients with anaphylaxis, and in particular, anaphylaxis in pregnancy (Australasian Society of Clinical Immunology and Allergy, 2020). The *Acute management of anaphylaxis in pregnancy* guidelines are intended for medical practitioners, midwives and nurses providing first responder emergency care, and are intended for use in conjunction with the 2021 *Acute Management of Anaphylaxis* guidelines available on the ASCIA website (Australasian Society of Clinical Immunology and Allergy, 2020).

ASCIA additionally advised that these guidelines have been endorsed by ASCIA, the Australasian College of Emergency Medicine (ACEM), the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), the College of Intensive Care Medicine of Australia and New Zealand (CICM), and the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG).

> *The prompt administration of adrenaline (epinephrine) is the cornerstone of anaphylaxis management in both the pregnant and non-pregnant population. A dose of 0.5mg adrenaline intramuscularly (IM) can be given for treatment of anaphylaxis in pregnancy.*

See the ASCIA *Acute management of anaphylaxis in pregnancy* guideline for detail at https://www.allergy.org.au/hp/papers/acute-management-of-anaphylaxis-in-pregnancy (Australasian Society of Clinical Immunology and Allergy, 2020).

Tick induced anaphylaxis treatment outcomes and follow up

When an anaphylaxis to a tick occurs, the treatment is the same as for anaphylaxis to any agent (Tick-induced Allergies Research and Awareness, n.d.-b; van Nunen, 2018; van Nunen & Ratchford, 2021). Oxygen and adrenaline are the mainstay in treatment of tick-induced anaphylaxis. Oral corticosteroids and antihistamines are usually given for use at home over the ensuing three days. A person who has suffered an anaphylactic episode will be given an authority prescription [for an adrenaline auto-injector] or instructions to see their family doctor as soon as possible for this purpose (Tick-induced Allergies Research and Awareness, n.d.-b).

In Rappo et al.'s retrospective analysis of patients presenting with tick bite at the ED at Mona Vale Hospital on Sydney's Northern Beaches, described above, of the 34 patients who were identified as cases of anaphylaxis overall, 76% of anaphylaxis cases (26 out of 34) received adrenaline during the course of their management, the majority of which was administered in the ED (Rappo et al., 2013). Rappo et al. noted, however, that almost one quarter of tick bite anaphylaxis cases did not receive any adrenaline as part of their management despite current guidelines suggesting that essential steps in the acute management of anaphylaxis should include a combination of adrenaline, supplemental oxygen and IV fluids (Australasian Society for Clinical Immunology and Allergy (2013) in Rappo et al., 2013).

The study found an H1-receptor blocker was given in 27 cases of anaphylaxis (IV or oral) and 10 patients were given a H2-receptor blocker. Seven patients were not given any antihistamine medication at all. All patients with anaphylaxis except one were treated with steroids in the ED (either prednisone or hydrocortisone). Rappo commented that 71% (24 out of 34) of the patients with anaphylaxis were discharged on three days of prednisone. Nine were given an epinephrine autoinjector and one was referred to their local medical officer for an epinephrine autoinjector Authority prescription. Ten of the patients with anaphylaxis were discharged with neither prednisone nor antihistamine (Rappo et al., 2013).

Only 53% (18 out of 34) of anaphylaxis cases were referred to an immunologist on discharge. Of these findings, Rappo et al. commented that while specialist immunologist follow up is also recommended to help prevent further episodes (Sampson et al. (2005), Brown et al. (2006), and Australasian Society for Clinical Immunology and Allergy (2013) in Rappo et al., 2013), approximately only half of the cases of tick bite anaphylaxis were referred to an immunologist. The authors also commented that the variation in the management observed in their study might reflect the under-recognition of the true incidence of tick bite anaphylaxis (Rappo et al., 2013).

Management of tick bites in people who are allergic to tick bites

It is vital that anyone with a known tick allergy summon urgent medical attention as soon as they are aware of an attached tick and not attempt to remove it without medical help. For patients with known tick allergies, removing the tick must occur in a medical facility with capacity to initiate advanced life support in the event of anaphylaxis (Australian Government Department of Health, 2020).

ASCIA's advice and recommendations, based on the clinical experience and published studies of medical specialists who treat patients with tick allergy, for people who are allergic to tick bites and who find a tick lodged in their skin, is as follows:

- If the person is allergic to ticks, they should carry an adrenaline (epinephrine) autoinjector (such as EpiPen®, Anapen®) and a mobile telephone. Symptoms of a severe allergic reaction (anaphylaxis) include any acute onset illness which evolves rapidly over minutes immediately after removing or disturbing only an adult tick, resulting in skin reactions such as welts or swellings, difficulty breathing, closing over of the throat, tongue swelling, impending loss of consciousness (faintness), sense of impending doom, or loss of consciousness.
- If the person is having symptoms of anaphylaxis as a reaction to a tick bite, use an adrenaline autoinjector, and follow the ASCIA Action Plan available on their website at https://www.allergy.org.au/hp/anaphylaxis/ascia-action-plan-for-anaphylaxis.
- Do not forcibly remove the tick.
- In a tick allergic person, the tick should be killed then removed from the patient [and both these steps should occur] in a hospital emergency department (Australasian Society of Clinical Immunology and Allergy, 2019b).

In 2021, van Nunen & Ratchford advised that, for self-management of tick anaphylaxis, any person who has had tick anaphylaxis previously should be supplied with an epinephrine autoinjector, and instructed in its use (van Nunen & Ratchford, 2021), and any further tick bite should be managed by the person as follows:

- Leave the tick undisturbed.
- Locate their epinephrine autoinjector.
- Telephone 000 for transport to the nearest ED.
- Not attempt to kill the tick or remove it at home.
- Have the tick killed *in situ* in the ED and leave it to drop off.
- If the tick is removed, this should be done by an expert in the ED using fine-tipped forceps.
- Avoid the use of plastic tweezers at the scene by ambulance officers, as these are inappropriate as they may compress the tick.
- Use their epinephrine autoinjector as instructed if indicated (van Nunen & Ratchford, 2021).

Additionally, the ASCIA Guidelines *Acute Management of Anaphylaxis 2021* (Section 10) advise that if there is a risk of re-exposure to allergens such as stings or foods, or if the cause of anaphylaxis is unknown (idiopathic), then it is important to prescribe and if possible dispense an adrenaline injector before discharge, pending specialist review (Australasian Society of Clinical Immunology and Allergy, 2021a). ASCIA also advises it is important to teach the patient how to use the adrenaline injector using a trainer device and provide them with an ASCIA Action Plan for Anaphylaxis, available at https://www.allergy.org.au/anaphylaxis. An Action Plan can be completed online and printed from the ASCIA website (Australasian Society of Clinical Immunology and Allergy, 2021a).

Additional advice from ASCIA (Australasian Society of Clinical Immunology and Allergy, 2019b), following consultation with a medical specialist, includes the following:

- A person with tick allergy may be able to kill and remove the tick safely without going to hospital. Some people with tick allergy are so highly allergic that medical support should always be sought. A medical specialist will advise as to which approach will be safest.
- If available, liquid nitrogen applied by a doctor is effective in killing a tick.
- If killing the tick and removing it can be safely performed by the person with tick allergy, kill the tick first by using a product to rapidly freeze the tick, to prevent it from injecting

more allergen-containing saliva. If the tick does not drop off, or the person cannot freeze the tick, leave the tick in place and summon urgent medical assistance to have the tick removed.

- Tick allergy should be confirmed by a clinical immunology/allergy specialist.

ASCIA also notes in its advice a link between tick allergy and the development of allergic reactions to mammalian meats and/or mammalian meat-derived gelatine.

Allergen immunotherapy (AIT), also known as desensitisation, is currently not available to switch off tick bite allergy (Australasian Society of Clinical Immunology and Allergy, 2019b).

Killing the tick *in situ* is aimed at ensuring the tick does not regurgitate allergen into the host and it is crucial to preventing allergic reactions. Preventing a recurrence of tick anaphylaxis is achievable by killing the tick *in situ* (van Nunen et al. (2014), Van Wye et al. (1991), and Stone (2000) in van Nunen, 2015).

Research in 2014 by van Nunen et al. investigated tick removal techniques in tick anaphylaxis sufferers (van Nunen et al. (2014) in van Nunen, 2015). van Nunen noted freezing ticks *in situ* with ether-containing agents is the most practicable method of killing a tick on a human host (van Nunen et al. (2014), and Australasian Society of Clinical Immunology and Allergy (2016) in van Nunen, 2018). It has the advantage of being easy to use and the sprays are readily available, whereas using fine-tipped forceps coupled with gentle upwards traction to remove ticks requires a great deal of skill and good eyesight (van Nunen, 2015).

Many patients with tick anaphylaxis report difficultly in visualising the tick (van Nunen, 2018), or being able to remove a tick with fine-tipped forceps (van Nunen, 2015). As such, the use of fine-tipped forceps should be restricted to health professionals in an appropriate facility and the use of household tweezers discouraged in the population at large (van Nunen, 2018). People almost invariably translate advice to use fine-tipped forceps to use household tweezers. This compresses the tick and its feeding chamber into the host's skin and thereby squeezes tick allergen into the host's vascular bed (van Nunen, 2018).

> *The tick must not be disturbed, scratched or pulled out as this is well recognised to result in an immediate anaphylaxis in those sensitised (Gauci et al. (1989), van Nunen et al. (2014), and Stone (2000) in van Nunen, 2015).*

The most recent study by Taylor et al. was a prospective cross-sectional study involving 121 patients, conducted in 2016 at Mona Vale Hospital Emergency Department (MVH ED) in Sydney, New South Wales (Taylor et al., 2019). Taylor et al. concluded the results supported the use of ether-containing spray and permethrin cream to kill ticks *in situ*, before careful removal by the mouthparts in order to reduce allergic and anaphylactic reactions (Taylor et al., 2019). That study also investigated the incidence of allergic/anaphylactic reactions when ticks were killed and removed from patients presenting to the MVH ED over a six-month period during peak tick season. Taylor et al. explained that the MVH ED sees an average of 20 tick bite presentations per month, and during peak tick season, more than 50 per month. It had been common practice at MVH ED for many years to kill nymph ticks with Lyclear® Scabies Cream (5% w/w permethrin, made in Belgium for Johnson & Johnson Pacific, Sydney, Australia) and adult ticks with Wart-Off Freeze® (dimethylether, Koninklijke Utermohlen NV, Wolvega, The Netherlands, distributed in Australia by Pharmacare Laboratories, Sydney, Australia). The authors noted both agents are well tolerated and approved by the Australian Therapeutic Goods Administration (TGA) for use on human skin

and that it is believed that killing ticks quickly with these agents immediately prevents further salivation and transmission of allergens (Taylor et al., 2019).

Unless contraindicated for medical reasons or patient refusal, the following methods were used to kill the ticks:

- Nymphs/Larvae: careful dab of Lyclear® Scabies Cream, covering the whole tick.
- Adult ticks: five sprays of Wart-Off Freeze®, held one cm above the tick.

Once the ticks have been killed, fine-tipped forceps were used to remove them by the mouthparts, avoiding compressing the abdomen, with Taylor et al. noting that, therefore, tick removal methods at MVH ED combine ASCIA recommendations (killing *in situ*) with the worldwide [other than Australia] consensus on early removal with fine-tipped forceps.

Of the 121 patients, 61 patients (28 were known to be tick hypersensitive) had ticks killed with either Wart-Off Freeze® or Lyclear® Scabies Cream (5% w/w permethrin) before removal with fine-tipped forceps or Tick Twister®, three (5%) of whom had allergic reactions although none was anaphylactic.

Forty four of the 61 patients had ticks killed with either ether-containing spray or permethrin cream in ED, before being removed with either fine-tipped forceps or Tick Twister®. Only one patient suffered an allergic reaction after removal; the datasheet in this case stated that the tick was particularly “embedded” making removal by mouthparts difficult. Taylor et al. noted that this patient had an allergic reaction despite the tick having been killed beforehand, highlighting the importance of still removing ticks by the mouthparts even after killing (Taylor et al., 2019).

Seventeen of the 61 patients presented to the ED having already killed ticks themselves with ether-containing spray or permethrin cream. All 17 patients had ticks then removed by the mouthparts; only two of the 17 patients suffered allergic reactions. These two patients had suffered reactions whilst attempting to use the ether-containing spray themselves prior to presentation, which Taylor et al. noted highlighted the importance of taking care when using this method (Taylor et al., 2019).

Taylor et al. explained that at MVH ED, the nozzle was held about one cm above the tick when the cold sprays are administered. Those attempting to replicate this method in the community need to be careful not to disturb ticks with the device. Since the device has a rounded aperture slightly larger than the tick and instructions for use on warts state to hold this flush with the skin, some may be tempted to try to fit the tick inside the device before spraying. This increases the chances of disturbing the tick. A new ether-containing spray – Medi Freeze Tick Off® (dimethylether, Pharmacare Laboratories Pty Ltd.) has both a wider aperture as well as instructions for use on ticks that advise holding at one cm above the skin for exactly this reason.

Nine patients who killed the tick with ether-containing spray in the community before self-removing ticks with either fingers or household tweezers, had allergic reactions, likely due to squeezing the abdomen of the tick during its removal. Taylor et al. concluded that within the limitation of their study, results supported the use of ether-containing spray and permethrin cream to kill ticks *in situ*, before careful removal by the mouthparts in order to reduce allergic and anaphylactic reactions. The authors commented their study supports the hypothesis that accidental tick disturbance, live tick removal with fingers or household tweezers and even

dead tick removal with fingers or household tweezers all increase the chance of risk of allergic reaction (Taylor et al., 2019).

Anaphylaxis resources

ASCIA provides a number of resources on anaphylaxis on its website (Australasian Society of Clinical Immunology and Allergy, 2021b). These include:

- Action Plans
- Checklists
- Adrenalin autoinjector information
- Anaphylaxis guidelines
- ASCIA anaphylaxis e-training courses
- Translations of anaphylaxis information
- General allergy information.

A&AA and TiARA also provide resources on anaphylaxis. See:

- A&AA, https://allergyfacts.org.au/
- TiARA, https://www.tiara.org.au/.

Mammalian meat allergy (MMA) after tick bites

MMA (also called alpha-gal syndrome (AGS), alpha-gal allergy, red meat allergy) is a serious, potentially life-threatening allergic reaction which may occur after people eat mammalian meat (van Nunen et al. (2007) in van Nunen, 2018) or are exposed to other products containing alpha-gal, and occurs after tick bite. The alpha-gal molecule has been identified in the saliva of certain species of ticks (Centers for Disease Control and Prevention, 2020; Fischer et al. (2020) in van Nunen & Ratchford, 2021).

Australian allergic diseases physicians were the first to describe a link between tick bites and the development of MMA. These findings have since been confirmed by researchers in the US and in Europe (Australasian Society of Clinical Immunology and Allergy, 2019b; van Nunen, 2018) and also in Asia, Central and South America, and Africa; that is, on all continents where humans are bitten by ticks (van Nunen, 2018; van Nunen & Ratchford, 2021).

MMA following tick bite was first reported in Australia by van Nunen et al. in 2007 in an abstract in the Internal Medicine Journal in which the authors described cases of 25 adults in Australia who developed red meat allergy after tick bites; 24 of the 25 patients who developed read meat allergy had a history of tick bite (van Nunen et al. (2007) in van Nunen, 2015, van Nunen et al. (2007) in 2018). Van Nunen et al. later published this work in the Medical Journal of Australia in 2009 (van Nunen et al. (2009) in van Nunen, 2015). Finding the association between tick bites and the development of MMA has proven to be the lynchpin in the prevention of MMA (Tick-induced Allergies Research and Awareness, 2019).

MMA is an emergent allergy that has become increasingly prevalent in tick-endemic areas of Australia and the US, and has been reported worldwide where *Ixodes* spp., *Amblyomma* spp. and *Haemaphysalis longicornis* ticks are endemic and known to bite humans (van Nunen,

2018). MMA has been reported in 18[5] countries, on every continent where humans are bitten by ticks (van Nunen & Ratchford, 2021).

In Australia, while the locations of reports of MMA after tick bite correlate with the distribution of *I. holocyclus,* the report of a case of MMA diagnosed in late 2016 in a man bitten by *Ixodes (Endopalpiger) australiensis* in Western Australia has suggested another tick species may be capable of inducing the condition (van Nunen, 2018). Indeed, Kwak et al. reported in 2018 that *Ixodes* (*Endopalpiger*) *australiensis* had been established as a second tick species associated with MMA in Australia (Kwak et al., 2018).

Unlike tick paralysis and tick anaphylaxis, where paralysis or anaphylaxis are only seen following the bite of an adult tick, in MMA, bites from either nymphs or adult ticks can provoke the condition (van Nunen, 2018). A single bite of a nymph tick may trigger MMA, as can bites from adult ticks (van Nunen & Ratchford, 2021).

TiARA advised the Parliamentary Inquiry (see Australian Parliamentary Inquiry into allergy and anaphylaxis) that as MMA is the only allergy globally where the trigger (a tick bite) is known, it therefore offers unparalleled opportunities for prevention when the following are considered:

- MMA does not occur without a tick bite.
- Not everyone bitten by a tick develops MMA.
- Not uncommonly, more than one person in a family will develop MMA.
- If a person is bitten by a tick and develops MMA, that person can more than double their allergy levels if they have a subsequent tick bite.
- If a person develops MMA and does not have another tick bite, that person can significantly reduce their allergy levels over 18 months or two years, with some people able to tolerate mammalian meats again after three to four years.
- If a person loses their MMA and has another tick bite, the MMA can return (Tick-induced Allergies Research and Awareness, 2019).

Developing sensitisation to allergen alpha-gal in mammalian meat has many potential consequences for people, mostly affecting the use of certain medical therapies, such as certain vaccines, heparin and cetuximab (van Nunen & Ratchford, 2021).

Alpha-gal (α-gal) and MMA

MMA is due to an IgE-mediated reaction to an allergen, a carbohydrate moiety, α-gal or alpha-gal (galactose-α-1,3-galactose) in the mammalian meat (Tick-induced Allergies Research and Awareness, 2019; Commins et al. (2009) in van Nunen, 2018). Alpha-gal is a most unusual allergen in that it has a greater propensity to provoke anaphylaxis than any other cross-reactive carbohydrate determinant (van Nunen, 2015). However, the allergic reaction in MMA is in contrast to tick anaphylaxis, which is due to the development of allergy antibody to tick salivary protein (Tick-induced Allergies Research and Awareness, 2019).

Alpha-gal is a sugar molecule, and is a constituent of the connective tissue of all mammals apart from humans, great apes and Old World monkeys (Galili et al. (1987), Galili et al. (1988), and Galili et al. (2004) in van Nunen, 2018; van Nunen & Ratchford, 2021) and is

[5] Dr Sheryl van Nunen advised MMA is currently reported in over 26 other countries, as at June 2022.

therefore present in all mammalian meat (and mammalian products) eaten by humans (van Nunen, 2018). In addition to not being found in humans, alpha-gal is also not found in fish, reptiles or birds (Centers for Disease Control and Prevention, 2020). Alpha-gal can be found in products made from mammals including some medications, cosmetics, vaccines, gelatine, and milk products (Centers for Disease Control and Prevention, 2020; van Nunen, 2015, 2018; van Nunen & Ratchford, 2021). Alpha-gal is known to be present in tick saliva in certain species of ticks (Centers for Disease Control and Prevention, 2020; Fischer et al. (2020) in van Nunen & Ratchford, 2021).

ASCIA advises that in addition to allergy to mammalian meats, some people will also be allergic to mammalian milks and to animal-derived gelatine, which is present in many food products, as a binding agent in some medications and in intravenous (IV) blood substitutes known as gelatine colloid (such as Haemaccel and Gelofusine) (Australasian Society of Clinical Immunology and Allergy, 2019b). Fortunately, these IV products are not usually used these days.

Following the initial report of MMA by van Nunen et al. in 2007, Commins et al. reported in 2009 on 24 patients with delayed anaphylaxis, angioedema or urticaria after consumption of red meat who possessed IgE specific for alpha-gal, more than 80% of whom reported being bitten by ticks before having symptoms (Commins et al. (2009) in van Nunen, 2015). Commins et al. and Platts-Mills et al. determined the molecular basis of MMA to be the epitope (alpha-gal) within the meat against which the specific IgE antibody is directed (Commins et al. (2009), and Commins et al. (2008) in van Nunen, 2018).

Subsequently, considerable data from Commins and colleagues, Platts-Mills and colleagues and international researchers has provided convincing evidence to confirm the observation by van Nunen et al in 2007 and 2009, of the development of MMA after tick bites (Jacquenet et al. (2009), Nuñez et al. (2011), Jappe (2012), Lee et al. (2013), Seklya et al. (2012), Hamsten et al. (2013), Michel et al. (2014), Wickner & Commins (2014), Shepherd (2015), Calamari et al. (2015), Gray et al. (2016), Chinuki et al. (2016), Cocco et al. (2017), Kologa et al. (2016), Lied (2017), Commins & Platts (2013), James et al. (2011), Kennedy et al. (2013), Mullins et al. (2012), Renaudin et al. (2012), Morisset et al. (2012), Morisset et al. (2013), Caponetto et al. (2013), Hamsten et al. (2013), Jappe et al. (2012), Baumgart et al. (2014), Platts-Mills & Commins (2013), and Fischer et al. (2015) in van Nunen, 2018).

Development of MMA in humans after tick bites

Van Nunen explained MMA in humans after tick bites is a process driven by genetic predisposition, environmental change and parasite-induced host immune changes, and probably an effect of the co-existence of an infectious agent in the tick (e.g. rickettsiosis) (van Nunen, 2018). This has resulted from the tick being forced by environmental change to take up residence on new hosts and subsequently making alpha gal in response to this change in the microbe exposure of the tick. Allergy to alpha-gal develops only in people who are predisposed and the allergy appears to be expressed more severely when relatively large amounts of alpha-gal enter the blood stream over a short period of time (van Nunen, 2015).

As alpha-gal is a foreign substance to humans, this allows humans who are predisposed after a tick bite to make a switch in production in B cells, making anti-gal antibodies from IgG manufacture to IgE production (Broady (2013), Dorey (1998), and Padula (2008) in van Nunen, 2018). Van Nunen further explained this process is facilitated by the galactosylation

of the tick proteins which enhances their immunogenicity. When the class switch to IgE production to the tick proteins is generated in the [human] host, alpha-gal-specific IgE is also made (Broady (2013), Dorey (1998), and Padula (2008) in van Nunen, 2018). Alpha-gal is then a cross-reactive carbohydrate determinant, in that allergic reactions occur after mammalian meat is consumed, as the person has become allergic to the alpha-gal injected by a tick (van Nunen, 2018).

Incidence of MMA

MMA is an emergent allergy which has now been reported in 18[6] countries worldwide on every continent where humans are bitten by ticks (van Nunen & Ratchford, 2021) The number of patients diagnosed with MMA has continued to rise (van Nunen, 2018).

MMA is exceedingly rare in adults in the absence of a prior tick bite (van Nunen, 2015).

Australia is the most affected country globally for MMA (van Nunen, 2018). Prevalence estimates for MMA published in 2016 indicate Australian tick-endemic regions have the highest prevalence globally (Fischer et al. (2016) in Kwak et al., 2018; Tick-induced Allergies Research and Awareness, 2019; van Nunen, 2018). van Nunen reported the following prevalence estimates:

- 113 out of 100,000 in the Sydney Basin, Australia
- 13 out of 100,000 in Virginia, US
- 4 out of 100,000 in Baden-Württemberg, Germany (Fischer et al. (2016) in van Nunen, 2018).

In tick endemic regions of the US and Germany, sensitisation rates (= allergy antibody production rates) have been established as being as high as 35%, with MMA symptoms occurring in only 8% to 9% (Tick-induced Allergies Research and Awareness, 2019; Fischer et al. (2017) in van Nunen, 2018; Fischer et al. (2016) in van Nunen & Ratchford, 2021), thus demonstrating the prevalence of alpha-gal-specific IgE sensitisation does not necessarily equate to clinical reactivity, as is the case with almost all allergens (van Nunen, 2018).

Van Nunen advises the number of diagnosed cases of MMA has continued to rise in Australia (van Nunen, 2018). As noted above in the international comparison of prevalence estimates in 2016, the estimated prevalence in the Sydney Basin was 113 out of 100,000. Earlier Australian data, in December 2013, indicated an estimated prevalence of 1 out of 880 (van Nunen (2014) in van Nunen, 2015), but with 2014 diagnoses included, prevalence was estimated to be 1 out of 550 at the time of van Nunen's publication in 2015 (van Nunen, 2015). Within the tick endemic areas of the Sydney basin, van Nunen noted that a diagnosis of MMA in adults, commonly anaphylaxis, appears to be as prevalent (estimate 0.12% and possibly higher) as the commonest food allergy in adults requiring adrenaline worldwide, with peanut allergy at 0.1% (Guglielmone et al. (2006) in van Nunen, 2015).

In Australia, the locations of previous reports of MMA after tick bite have correlated with the distribution of I. holocyclus (Kwak et al., 2018; van Nunen, 2015). About 50% of Australians are potentially exposed to bites from this species and I. holocyclus is responsible for 95% of tick bites in humans in Australia (van Nunen et al. (2013) in Kwak et al., 2018; Tick-induced

[6] Dr Sheryl van Nunen advised MMA is currently reported in over 26 other countries, as at June 2022.

Allergies Research and Awareness, 2019). With the description of Ixodes (Endopalpiger) australiensis as the second tick species as a cause of MMA in Australia, potential exposure of the Australian population to ticks associated with MMA has increased to about 60% (Tick-induced Allergies Research and Awareness, 2019).

TiARA advised in its submission to the 2020 Parliamentary Inquiry (see Australian Parliamentary Inquiry into allergy and anaphylaxis) that:

- the majority of tick anaphylaxis sufferers develop alpha-gal specific IgE and at least 30% develop MMA symptoms as well
- statistics indicate that in tick endemic regions in Australia, up to 25% of the community will have alpha-gal specific IgE and be unaware of their sensitisation [as they have no symptoms when eating mammalian meat or are not mammalian meat eaters. The risk of reaction to mammalian products in medications still exists for these people]
- individuals may be unaware of having been bitten by a tick particularly if the bite has been from a nymphal tick (2mm and resembling a tiny splinter), as people may not recognise this stage as being a tick, or ticks may be removed without being recognised as being ticks when the individual is not tick-aware (i.e. is visiting from non-tick endemic regions) (Tick-induced Allergies Research and Awareness, 2019).

In addition to the information by TiARA, van Nunen & Ratchford noted that, after two tick bites, up to 50% of individuals may be sensitised to alpha-gal (Kaneko et al. (2019) in van Nunen & Ratchford, 2021). Also, regarding some individuals being unaware of having been bitten by a tick (van Nunen et al. (2013) in van Nunen & Ratchford, 2021) this can potentially happen if they are visitors rather than residents in tick-hyperendemic areas. Van Nunen and Ratchford highlighted such areas as the Northern Beaches area of Sydney, Maleny in Queensland, Denmark in Western Australia, and [generally down the eastern seaboard of Australia as far as] Lakes Entrance in Victoria (van Nunen & Ratchford, 2021).

Ticks that cause or provoke MMA after tick bite

MMA is an emergent allergy that has become increasingly prevalent in tick-endemic areas of Australia and the US, and has been reported worldwide where *Ixodes* spp., *Amblyomma* spp. and *Haemaphysalis longicornis* ticks are endemic and known to bite humans (van Nunen, 2018). MMA has been reported in 18[7] countries, on every continent where humans are bitten by ticks (van Nunen & Ratchford, 2021). To date, in each of these countries, apart from Australia, bites from only a single tick species have been linked to the development of MMA.

The confirmed tick species are:

- *I. holocyclus* (Australian paralysis tick) in Australia
- *Amblyomma americanum* (lone star tick) in the US
- *I. ricinus* (castor bean tick) in Europe
- *Ixodes cajennense* (cayenne tick) in Panama (Kwak et al., 2018).

Ticks suspected of provoking MMA after tick bite are:

- *Ixodes nipponensis* (a common cattle tick) in Japan and Korea
- *Amblyomma sculptum* in Brazil

[7] Dr Sheryl van Nunen advised MMA is currently reported in over 26 other countries, as at June 2022.

- *Amblyomma variegatum* (tropical bont tick) in the Ivory Coast
- *Haemaphysalis longicornis* (Asian longhorned tick or bush tick) in Japan.

Other tick species remain to be identified in South Africa (Kwak et al., 2018).

In Australia, while the locations of reports of MMA after tick bite correlate with the distribution of *I. holocyclus,* the report of a case of MMA diagnosed in late 2016 in a man bitten by *Ixodes (Endopalpiger) australiensis* in Western Australia has suggested another tick species may be capable of inducing the condition (van Nunen, 2018). Indeed, Kwak et al. reported in 2018 that *Ixodes* (*Endopalpiger*) *australiensis* had been established as a second tick species associated with MMA in Australia (Kwak et al., 2018).

Hypothesis for increasing prevalence of MMA

Van Nunen notes the increasing prevalence of MMA in Australia and the US could most reasonably be explained by the increase in host numbers [for ticks], with bandicoots and other small native mammals flourishing in Australia (van Nunen (2014) in van Nunen, 2015), along with rabbits (Taylor et al., 2020) and black rats (Lydecker et al., 2014) being observed as hosts for Australian paralysis tick (*I. holocyclus*). In the southeastern US, there has been an increase in the population of the white-tailed deer (James et al. (2011) in van Nunen, 2015). Modelling the effects of global warming has indicated higher tick exposure will occur in the future (Tick-induced Allergies Research and Awareness, 2019). Please refer to the *Introduction to ticks, Australian ticks and tick-borne diseases and illnesses* Guidance Note for further information on the increase in geographic spread of the main tick species internationally.

Demographics

Van Nunen notes the clinical features of MMA are well defined and MMA is known to affect both adults and children (van Nunen, 2015). Regarding MMA in children, van Nunen cited four studies (Kennedy et al. (2013), van Nunen et al. (2007), van Nunen et al. (2009), and Caponetto et al. (2013) in van Nunen, 2015), and noted Caponetto et al. had concluded that MMA is not uncommon in children and that it mirrors their experience in adults (Caponetto et al. (2013) in van Nunen, 2015). In the US, while both children and adults have been diagnosed with alpha-gal syndrome, most cases have been reported in adults (Centers for Disease Control and Prevention, 2020).

Geographical distribution

Van Nunen reports that cases have now been reported from the following continents and countries, with Australia the first to report MMA in 2007, and Brazil and Norway the most recent, in 2017:

- Australia (van Nunen et al. (2007), van Nunen et al. (2009), Mullins et al. (2012), and Baumgart et al. (2014) in van Nunen, 2018).
- North America
- the US (Commins et al. (2009), and Kennedy et al. (2013) in van Nunen, 2018), with most cases of alpha-gal reported to date have been among people living in the southeastern US (Centers for Disease Control and Prevention, 2020).
- Central America
- Panama (Wickner & Commins (2014) in van Nunen, 2018).

- South America
- Brazil (Cocco et al. (2017) in van Nunen, 2018).
- Europe
- France (Jacquenet et al. (2009), Renaudin et al. (2012), Morisset et al. (2012), and Morisset et al. (2013) in van Nunen, 2018)
- Spain (Nuñez et al. (2011) in van Nunen, 2018)
- Germany (Jappe (2012), Caponetto et al. (2013), and Jappe et al. (2012) in van Nunen, 2018)
- Switzerland (Michel et al. (2014) in van Nunen, 2018)
- Sweden (Hamsten, Tran et al. (2013), and Hamsten, Stakhammar et al. (2013) in et al. van Nunen, 2018)
- The United Kingdom [Scotland] (Shepherd (2015) in van Nunen, 2018)
- Italy (Calamari et al. (2015) in van Nunen, 2018)
- Norway (Lied (2017) in van Nunen, 2018).
- Asia
- Korea (Lee et al. (2013) in van Nunen, 2018)
- Japan (Seklya et al. (2012), and Chinuki et al. (2016) in van Nunen, 2018).
- Africa
- [Republic of] South Africa (Gray et al. (2016) in van Nunen, 2018)
- Ivory Coast (Kaloga et al. (2016) in van Nunen, 2018).

More recently, in 2021, van Nunen and Ratchford noted MMA had been reported from 18 countries, on every continent where human are bitten by ticks (van Nunen & Ratchford, 2021), although TiARA advised that as at May 2021, MMA has been reported in 22[8] countries.

In Australia, cases have been reported all along the eastern seaboard. Cases have also been reported in patients from areas where ticks are nonendemic, as a result of recreational exposures to ticks among individuals resident in these nonendemic areas (van Nunen, 2015). Van Nunen highlighted that in 2015 the distribution of reported cases in Australia reflects the known distribution of *I. holocyclus* (van Nunen, 2015).

Particular “hotspots” along the coast remote from the Sydney basin were noted by van Nunen to include:

- the hinterland around Noosa [Maleny] in Queensland, Australia
- the south coast of New South Wales, Australia (van Nunen, 2015).

Van Nunen and Ratchford noted that while MMA does not occur in the absence of a tick bite, some individuals may be unaware of having been bitten by a tick (van Nunen et al. (2013) in van Nunen & Ratchford, 2021), with this potentially happening if they are visitors rather than residents in tick-hyperendemic areas (e.g. the Northern Beaches area of Sydney, Maleny in Queensland, Denmark in Western Australia, and [generally down the eastern seaboard of Australia as far as] Lakes Entrance in Victoria) (van Nunen & Ratchford, 2021).

[8] Dr Sheryl van Nunen advised that, as at June 2022, MMA is currently reported in over 26 other countries.

Symptoms of MMA

Adults and children with MMA after tick bites have similar symptoms and clinical presentation, ranging from angioedema or gut symptoms alone to life-threatening anaphylaxis, with severe allergic reactions being more common at 65.5% (Fischer et al. (2016), and Kennedy et al. (2013) in van Nunen, 2018).

MMA symptoms often do not commence until a few weeks after the tick bite(s).

The Centers for Disease Control and Prevention provides the following advice on the symptoms of alpha-gal syndrome (or MMA) (Centers for Disease Control and Prevention, 2020):

- Alpha-gal syndrome (AGS) reactions can include:
- rash
- hives
- nausea or vomiting
- difficulty breathing
- drop in blood pressure
- dizziness or faintness
- severe stomach pain.
- Symptoms commonly appear three to six hours after eating meat or exposure to products containing alpha-gal (e.g. gelatine-coated medications).
- Reactions can be different from person to person and can range from mild to severe or even life-threatening.
- People may not have an allergic reaction after every alpha-gal exposure.
- A person who thinks they may have AGS (MMA) should talk to a doctor (Centers for Disease Control and Prevention, 2020).

For information by A&AA on 'Signs and symptoms of allergic reaction', 'EpiPen® administration, and 'Anapen® administration', go to https://allergyfacts.org.au/resources/videos-from-a-aa.

Clinical and other features of MMA after tick bite

Adults and children with MMA after tick bites have similar clinical findings (van Nunen, 2018). MMA may manifest as anaphylaxis, recurrent angioedema or gut symptoms after ingestion of mammalian meat with symptoms typically delayed by three to six hours (van Nunen (2015), van Nunen (2014), van Nunen et al. (2007), van Nunen et al. (2009), and Commins et al. (2009) in van Nunen, 2018). The delay of three to six hours is due to factors modulating the uptake of the allergen (alpha-gal) from the gut and its subsequent presentation to the host circulation (van Nunen (2015), and Commins et al. (2008) in van Nunen, 2018). Van Nunen explained that alpha-gal is present on both glycoproteins and glycolipids (including chylomicrons) (van Nunen, 2018). Fat digestion takes several hours and during this time alpha-gal-containing chylomicrons are absorbed by the enterocytes, transported to the lymphatics and then enter the circulation via the thoracic duct, triggering basophil mediator release (Commins et al. (2014) in van Nunen, 2018) when they reach the circulation (van Nunen, 2018).

While clinical findings range from angioedema or gut symptoms alone to life-threatening anaphylaxis, severe allergic reactions are more common at 65.5% (Fischer et al. (2016), and Kennedy et al. (2013) in van Nunen, 2018).

Clinical and other features of MMA after tick bite include:

- patients with a history of tick bites present with allergic reactions after ingesting mammalian meat (or meat products) – reactions are typically delayed (i.e. “middle of the night” anaphylaxis) and often severe (van Nunen et al. (2009), Nuñez et al. (2011), Lee et al. (2013), Seklya et al. (2012), Hamsten, Tran et al. (2013), Michel et al. (2014), Wickner & Commins (2014), Fischer et al. (2016), Kennedy et al. (2013), Renaudin et al. (2012), Hamsten, Starkhammar et al. (2013), Fischer et al. (2015) in van Nunen, 2018). The anaphylaxis that evolves rapidly and is often severe is due to intravascular basophil activation (Crispell et al. (2019) in van Nunen & Ratchford, 2021)
- the interval between mammalian meat ingestion and allergic reaction is two to 10 hours, usually three to six hours depending on exposure to co-factors/amplifying factors (e.g. alcohol or exercise) (Commins et al. (2009), Jacquenet et al. (2009), Fischer et al. (2016), Renaudin et al. (2012), Morisset et al. (2012), Morisset et al. (2013), and Fischer et al. (2015) in van Nunen, 2018)
- anaphylaxis occurs in up to 60% of patients, delayed urticaria or angioedema features and gut symptoms may occur alone (van Nunen et al. (2007), van Nunen et al. (2009), Commins et al. (2009), Nuñez et al. (2011), Hamsten, Tran et al. (2013), Wickner & Commins (2014), Shepherd (2015), Calamari et al. (2015), Fischer et al. (2016), Kennedy et al. (2013), Renaudin et al. (2012), and Hamsten, Starkhammar et al. (2013) in van Nunen, 2018)
- there is a history of tick bite. Occasionally, evidence for the tick bite can be obscure or subtle (e.g. a recalled excoriated scalp lesion consistent with a tick bite after only a single visit to a tick endemic area) (van Nunen et al. (2013) in van Nunen, 2018)
- a history of a large local reaction to a tick bite is not uncommon (van Nunen et al. (2007), van Nunen et al. (2009), and Fischer et al. (2015) in van Nunen, 2018)
- bites from either nymphs or adult ticks may provoke the condition (van Nunen, 2018; van Nunen & Ratchford, 2021)
- individuals with MMA will almost invariably have alpha-gal-specific IgE detectable in their serum, and/or positive skin tests to raw, organic mammalian meats and/or cetuximab (van Nunen et al. (2007), van Nunen et al. (2009), Commins et al. (2009), Jacquenet et al. (2009), and Michel et al. (2014) in van Nunen, 2018).

Amplifying factors (co-factors) in MMA

Van Nunen noted that the interval between mammalian meat ingestion and allergic reaction is two to 10 hours, usually three to six hours depending on exposure to co-factors/amplifying factors (e.g. alcohol or exercise) (van Nunen, 2018).

Co-factors/amplifying factors play a crucial role in triggering a reaction in patients with MMA, an understanding of which is important in ensuring a patient’s safety (van Nunen, 2018). In MMA, the effect of co-factors is so striking that van Nunen notes European authors have drawn parallels with food-dependent exercise-induced anaphylaxis (Fischer et al. (2016), and Morisset et al. (2012) in van Nunen, 2018).

Van Nunen also noted that modulating factors all separately and collectively confer an increased risk of an alpha-gal-sensitised person having an allergic reaction to mammalian meat at any particular time, as is the case with all food allergens, to a greater or lesser

degree (Fischer et al. (2016), Morisset et al. (2012), Wölbing et al. (2013), and Versluis et al. (2016) in van Nunen, 2018).

Modulating co-factors/amplifying co-factors reported by van Nunen in 2018, and van Nunen and Ratchford in 2021 include (Fischer et al. (2016), Morisset et al. (2012), Wölbing et al. (2013), and Versluis et al. (2016) in van Nunen, 2018; Morriset et al. (2012), Wölbing et al. (2013), Versluis et al. 2016), and Dua et al. (2019) in van Nunen & Ratchford, 2021):

- ingesting a greater amount of allergen (mammalian meat or meat product)
- the effect of cooking (slow cooking or reheating of the meat dish breaks down the connective tissue in meat, increasing alpha-gal availability)
- offal consumption (e.g. sausage encasings, liver, kidney), because offal contains higher concentrations of the alpha-gal allergen
- co-ingestion of alcohol
- sleep deprivation
- exercise, particularly within two hours
- inclusion of spices, usually chilli and capsicum (but not nutmeg, black pepper or bay leaf)
- prior administration of non-steroidal anti-inflammatory agents (within 24 hours)
- being otherwise unwell/recent illness (e.g. upper respiratory tract infection)
- being in the premenstrual/perimenstrual phase.

Different mammalian meat products have variable concentrations of alpha-gal, with offal (e.g. pork kidney) having the highest alpha-gal concentration (Morisset et al. (2012) in van Nunen, 2018), thus increasing the likelihood of a reaction (van Nunen, 2018). In contrast, pasteurised cow's milk is often tolerated, as while cow's milk contains alpha-gal, boiling the milk abolishes alpha-gal reactivity (Commins et al. (2014) in van Nunen, 2018).

Differential diagnosis and pitfalls in diagnosing MMA

The prominent role of co-factors in triggering episodes of MMA can make its diagnosis difficult (van Nunen, 2018). As is the case with almost all allergens, van Nunen highlighted that the prevalence of alpha-gal-specific IgE sensitisation does not necessarily equate to clinical reactivity (van Nunen, 2018). A study in Germany found that of the 35.0% of forest workers and hunters who were sensitised to alpha-gal (alpha-gal-specific IgE > 0.10 kUA/L), only 8.6% have had MMA symptoms (Fischer et al. (2017) in van Nunen, 2018).

Van Nunen reported the following pitfalls in the diagnosis of tick bite-induced MMA:

- Lack of awareness in doctor or patient of the existence of the condition (axiom: where certain tick species are endemic and humans are bitten, MMA will occur).
- Interpreting the presence of alpha-gal-specific IgE (in the absence of supportive clinical history) as indicating the patient has a clinical allergy to mammalian meat. The presence of allergen-specific IgE in serum or a positive skin test to any allergen does not equate to the patient having an allergy to that allergen, unless it can be established clinically that the allergen is causing the symptoms being experienced at this time in their life. Alpha-gal sensitisation may be present in the absence of clinical allergy to mammalian meats (Fischer et al. (2016) in van Nunen, 2018).
- MMA is an "any time" but not an "every time" allergy (i.e. co-factors are very influential in its expression) (Fischer et al. (2016), Morisset et al. (2013), and Fischer et al. (2015) in van Nunen, 2018).

- Challenge design is difficult due to delayed reactions and the crucial role of co-factors (Fischer et al. (2016), Morisset et al. (2013), and Fischer et al. (2015) in van Nunen, 2018).

Diagnosis of MMA following tick bites

The prominent role of co-factors in triggering episodes of MMA can make its diagnosis difficult (van Nunen, 2018). As is the case with almost all allergens, van Nunen highlighted that the prevalence of alpha-gal-specific IgE sensitisation does not necessarily equate to clinical reactivity (van Nunen, 2018).

Current advice from ASCIA regarding confirming a diagnosis of tick allergy includes advice on tests for MMA. ASCIA notes researchers have identified that the following blood allergy tests are positive in the majority of people with serious allergic reactions to tick bites. The following blood tests for allergen specific IgE may assist in confirming a diagnosis:

- Mammalian meats Immunocap.
- Alpha-galactose Immunocap. Alpha-galactose is a sugar molecule present in meat from mammals other than humans, great apes and Old World monkeys. It is also found in the gut of ticks.
- Blood tests for mast cell tryptase may also be useful. Tryptase is an enzyme that is increased in people with a condition called mastocytosis. It is associated with a higher risk of allergic reactions to many allergic triggers including insect stings and tick bites. People with higher tryptase levels may have more severe anaphylactic reactions to insect stings and bites (Australasian Society of Clinical Immunology and Allergy, 2019b).

More recently, in 2021, van Nunen and Ratchford provided advice on the diagnosis and management of MMA, including a diagnostic tree/pathway (van Nunen & Ratchford, 2021).They noted that diagnosis of MMA anaphylaxis depends on clinical features. Additionally, radioallergosorbent (RAS) measurement of allergen-specific IgE levels against alpha-gal, beef, lamb, pork and bovine gelatine is recommended at diagnosis as a baseline to facilitate future advice, and that measurement of the convalescent tryptase level is important to exclude coincident mastocytosis (van Nunen & Ratchford, 2021).

Management of MMA

Management of MMA includes dietary education, therapeutic precautions, prevention of tick bites, and killing the tick *in situ* to prevent allergic reactions to tick bites (van Nunen, 2018). Treatment of mammalian meat anaphylaxis is non-specific and the same for any patient with anaphylaxis. The provision of an epinephrine autoinjector, instruction in its use and an anaphylaxis action plan are essential (van Nunen & Ratchford, 2021).

Patient education for people with MMA is essential and includes (van Nunen & Ratchford, 2021):

- prevention and management of further tick bites
- the risk of alpha-gal sensitisation.
- Provided the person has not had further tick bites, they may be able to reintroduce mammalian meat after several years; reintroduction should be guided by a reduction in alpha-gal sIgE levels (Mabelane et al. (2018) in van Nunen & Ratchford, 2021).

Dietary education

Van Nunen and Ratchford advised that patients diagnosed with MMA will require dietary advice from an accredited practising dietician, with additional information available to patients at TiARA (www.tiara.org.au in van Nunen & Ratchford, 2021).

People with allergic reactions to mammalian meats are advised to avoid all mammalian meats (beef, lamb/mutton, pork, goat, horse, kangaroo, venison and other exotic mammals). Artificial blood (made from beef), and all forms of gelatine should also be avoided (Australasian Society of Clinical Immunology and Allergy, 2019b).

TiARA advises that, in addition to avoidance of all mammalian meats, in some instances, cow's milk and cow's milk products may also need to be avoided (Tick-induced Allergies Research and Awareness, n.d.-b). In a minority of patients with MMA who are allergic to cow's milk or mammalian gelatine, identifying hidden sources of cow's milk and gelatine is essential for their safety (www.allergy.org.au, and www.allergyfacts.org.au in van Nunen, 2018). Van Nunen and Ratchford also noted that a minority of people who have experienced mammalian meat anaphylaxis will also react to mammalian milk and milk products, typically reacting to soft cheeses and cheeses containing animal rennet (in some imported cheeses) but tolerate hard cheeses. As such, mammalian milks and their products should only be excluded if they cause symptoms at any stage (van Nunen & Ratchford, 2021).

Regarding gelatine, evidence indicates that patients who are negative for sIgE to bovine gelatine usually tolerate oral gelatine, however, parenteral gelatine, such as in certain vaccines, should usually be avoided (Mullins et al. (2012) in van Nunen & Ratchford, 2021).

Some individuals with mammalian meat anaphylaxis have been reported to also react to mammalian meat vapours (e.g. barbeque meat fumes) (Turner et al. (2011) in van Nunen & Ratchford, 2021).

In addition to the specifics about what foods/drinks should/may need to be avoided in patients with MMA, a dietary review focussing on iron uptake and ensuring overall nutritional adequacy is also advised (Tick-induced Allergies Research and Awareness, n.d.-b).

Therapeutic precautions

ASCIA advises that people with mammalian meat allergy should wear a medical bracelet warning of allergy to intravenous gelatine colloid. This is an intravenous preparation used as a blood substitute in emergency situations (Australasian Society of Clinical Immunology and Allergy, 2019b). Its use has declined in Australia.[9]

Before initiating treatment with certain therapeutic agents (e.g. cetuximab, gelatine-containing substances, bovine artificial blood), clinicians should undertake a careful assessment of the risk of anaphylaxis, including serological analysis for alpha-gal-specific IgE in any individual who works, lives, volunteers or undertakes recreation in a tick endemic area, particularly where a history is obtained of a tick bite prior, or of mammalian meat or gelatine allergy (van Nunen, 2015).

[9] Advice from TiARA, as at May 2021.

Alpha-gal is widely distributed in therapeutic agents, with exposures to alpha-gal-containing medications having proved lethal in a minority of people (van Nunen, 2018). In people who are sensitised to alpha-gal, several novel therapeutic opportunities, such as wound healing and tumour therapy advances, may prove risky (Galili (2013) in van Nunen, 2018). These therapeutic opportunities are described below.

Cetuximab

Cetuximab is a murine-derived cancer therapy that has the potential for anaphylaxis in patients with alpha-gal sensitisation and MMA (Lauer et al. (2019), and Yuile et al. (2020) in van Nunen & Ratchford, 2021). Due to its alpha-gal content, fatal reactions have occurred (Pointreau et al. (2012) in van Nunen, 2018). In Australia, risk of anaphylaxis with cetuximab use in Northern Sydney is 6.9%, with 59 cases, including two fatalities having been reported to the TGA Database of Adverse Event notification up to July 2020 (Lauer et al. (2019), and Yuile et al. (2020) in van Nunen & Ratchford, 2021). Both physicians and pharmacists need to inform meat allergic patients of the risks inherent in taking cetuximab. The risk of fatal anaphylaxis is well documented and well known to allergic diseases physicians but van Nunan cautions this risk still needs to be known by patients before they receive therapy with cetuximab (van Nunen, 2015).

Vaccination

Some vaccines, for example, measles-mumps-rubella and zoster [Zostavax, but not Shringrix],[10] have measurable levels of alpha-gal, and other vaccines may contain mammalian products (Stone et al. (2017) in van Nunen, 2018). Use of these vaccines may expose patients with alpha-gal-specific IgE to the risk of an allergic reaction (Schmidle et al., 2021; Stone et al. (2017) in van Nunen, 2018). Usually a different brand of vaccine can be found for the vaccination (Schmidle et al., 2021). Schmidle et al. noted in their 2021 article that recent case reports had pointed to severe anaphylaxis in patients suffering from alpha-gal syndrome after vaccination with vaccines containing hydrolysed gelatin (Schmidle et al., 2021). In their study Schmidle et al. evaluated if basophil activation tests (BATs) performed with such vaccines (Varicella, Zoster, Measles, Mumps, and Rubella were tested) were positive in patients with alpha-gal syndrome. Of this evaluation, the authors concluded that gelatine-containing vaccines should be administered with caution or avoided in patients with alpha-gal syndrome because of their high potential to activate basophils, indicating a risk for anaphylaxis. They also concluded that BATs is a useful additional tool for screening for potentially high-risk alpha-gal-containing drugs (Schmidle et al., 2021). Regarding whether a list of vaccines that contain alpha-gal is available, Schmidle et al. noted that, to date, information on the exact source and concentration of gelatine in vaccines is only available upon personal request and communication with the companies (Pinson & Waibel (2015) in Schmidle et al., 2021). Additionally, evidence suggested the source and concentration of gelatine – and therefore quantities of alpha-gal – might vary between countries, as different drugs from different companies are available on the market (Wedi (2017) in Schmidle et al., 2021). However, Schmidle et al. noted this information could be very useful to identify potentially “dangerous” vaccines for patients with alpha-gal syndrome and therefore be life-saving. Additionally, Schmidle et al. noted that as vaccines such as the varicella (chickenpox)

[10] Updated information provided by the author in May 2021.

VZ vaccine are especially used in older patients who are the population that is mainly affected by alpha-gal syndrome (Fischer et al. (2020) in Schmidle et al., 2021), “makes this point even more important” (Schmidle et al., 2021).

Indeed, van Nunen and Ratchford noted that gelatine containing vaccines such as Zostavax can cause anaphylaxis as indicated by one formal and several anecdotal reports (Stone et al. (2017) in van Nunen & Ratchford, 2021).

ASCIA provides advice about the COVID 19 vaccines currently available in Australia, with advice updated in February 2022. See https://www.allergy.org.au/patients/ascia-covid-19-vaccination-faq. ASCIA advises there is no food, gelatin or latex in the COVID-19 vaccines that are currently available, and they are not grown in eggs. ASCIA advises the COVID 19 vaccines available in Australia are safe for people with immune system disorders, including allergy, immunodeficiency or autoimmune conditions. These COVID 19 vaccines are:

- Pfizer/BioNTech Comirnaty mRNA-based COVID-19 vaccine – available in Australia for adults and children five years and over
- Moderna Spikevax mRNA-based COVID-19 vaccine – available in Australia for adults and children six years and over
- AstraZeneca/Oxford Vaxzevria viral vector COVID-19 vaccine – available in Australia for adults 18 years and over
- Novavax/Biocelect Nuvaxovid spike protein based COVID-19 vaccine - available in Australia for adults 18 years and over (approved January 2022). (Australasian Society of Clinical Immunology and Allergy, 2022).

Gelatine

Alpha-gal can be found in products made from mammals including gelatine (Centers for Disease Control and Prevention, 2020; Mullins et al., 2016). Sources of gelatine in therapeutic opportunities may need flagging, for example, vaccines (see section on ‘Vaccination’ above), capsules, tablets, suppositories, and collagen-containing agents, including implants (Mullins et al. (2012) in van Nunen, 2018). Fewer than 10% of patients who are allergic to mammalian meat also react to gelatine (van Nunen, 2018). Patients who are negative for sIgE to bovine gelatine usually tolerate oral gelatine, however, parenteral gelatine, such as in certain vaccines, should usually be avoided (Mullins et al. (2012) in van Nunen & Ratchford, 2021).

Porcine heart valve protheses

Alpha-gal has been identified and quantified in porcine heart valve bio-prostheses (Naso et al. (2013) in van Nunen, 2015); alpha-gal sensitisation likely played a role in serious allergic events after porcine cardiac valve xenograft transplantation (Naso et al. (2013), Fournier et al. (2011), and Mozzicato et al. (2014) in van Nunen, 2018).

TAVI (Trans-catheter Aortic Valve Implantation) is performed using beef pericardium. No information is available regarding the risk of allergic reaction for this procedure to date, although evidence on sensitisation to alpha gal is expected to be published in the near future.

Antivenoms

Antivenoms to snake (Fischer et al. (2017) in van Nunen, 2018), redback and funnel web spider, box jellyfish and stonefish venoms along with other antivenoms produced internationally (all made in mammals) may confer a risk of reaction (van Nunen, 2018).

Alpha-gal sensitisation and atherosclerosis

Two recent studies have investigated whether there is an association between alpha-gal sIgE and atherosclerotic coronary artery disease (Wilson et al. (2018), and Vernon et al. (2020) in van Nunen & Ratchford, 2021). This research is emerging, and while both studies identified associations, they also noted further follow up research is needed, including in larger studies and to investigate potential mechanistic pathways. However, from this preliminary research, van Nunen and Ratchford cautioned that tick bite prevention and management campaigns will be even more important to keep Australians safe from the sequelae of tick bites (van Nunen & Ratchford, 2021).

Within this emerging research area, two studies published in 2022 also reported associations between alpha-gal IgE and coronary artery disease (Pattarabanjird et al., 2022; Vernon et al., 2022).

The study by Pattarabanjird et al. (2022), involving 60 patients, 17 (28%) of who were positive for IgE to alpha-gal, identified CCR6+ class-switched memory (SWM) B cells as potential producers of IgE to alpha-gal in patients with coronary artery disease. The authors concluded their results may have important implications for a better understanding of, and better therapeutic approaches for, patients with IgE sensitization to alpha-gal (Pattarabanjird et al., 2022).

The study by Vernon et al. (2022) was cross-sectional analysis of participants enrolled in the BioHEART cohort study which identified that alpha-gal sensitization was independently associated with noncalcified plaque burden and obstructive coronary artery disease and this occurred at higher frequency in patients with ST-segment–elevated myocardial infarction (STEMI) than those with stable or no coronary artery disease. The authors noted their findings have substantial public health implications given the high rates of alpha-gal sensitization in tick-endemic areas globally (Vernon et al., 2022). They also noted their findings warrant further investigations to unravel potential disease mechanisms and pathways, as well as to elucidate potential roles in cardiovascular risk assessments and prevention programs, particularly in tick endemic areas (Vernon et al., 2022).

Effect of subsequent tick bites on allergy levels in individuals with MMA

Finding the association between tick bites and the development of MMA has proven to be the lynchpin in the prevention of MMA (Tick-induced Allergies Research and Awareness, 2019).

Tick bite-induced allergies including MMA are often severe, and should largely be avoidable, with preventing tick bites key to preventing tick-induced allergies (van Nunen, 2015, van 2018).

TiARA notes that as MMA is the only allergy globally where the trigger (a tick bite) is known, it therefore offers unparalleled opportunities for prevention when the following are considered:

- MMA does not occur without a tick bite.
- Not everyone bitten by a tick develops MMA.
- Not uncommonly, more than one person in a family will develop MMA.
- If a person is bitten by a tick and develops MMA, that person can more than double their allergy levels if they have a subsequent tick bite.

- If a person develops MMA and does not have another tick bite, that person can significantly reduce their allergy levels over 18 months or two years, with some people able to tolerate mammalian meats again after three to four years.
- If a person loses their MMA and has another tick bite, the MMA can return (Tick-induced Allergies Research and Awareness, 2019).

Please refer to the *Prevention and management of tick bites in Australia* Guidance Note for advice on how to prevent tick bites.

Preventing MMA by killing ticks in situ

Killing the tick *in situ* using ether-containing sprays and avoiding any compression of the tick when it is removed is aimed at ensuring the tick does not regurgitate allergen into the host. This technique significantly limits the possibility of tick-induced allergies occurring, including MMA and tick anaphylaxis (van Nunen et al. (2014), and Australasian Society of Clinical Immunology and Allergy Tick allergy (2016) in van Nunen, 2018). Please refer to the *Prevention and management of tick bites in Australia* Guidance Note for advice on how to kill ticks *in situ.*

MMA in individuals with the co-existing condition of mastocytosis

Approximately 3% to 4% of people with MMA after tick bites have co-existing mastocytosis (Tick-induced Allergies Research and Awareness, n.d.-b). Mastocytosis is a very rare disease in which an increased number of mast cells (histamine releasing cells which result in the inflammation seen in allergic reactions) are made in the bone marrow. Allergens and other agents provoke mast cells to release histamine and profound anaphylaxis results due to the increased numbers of mast cells. This condition must be checked for in any individual who has a profound anaphylaxis, whatever the agent. Education for other essential triggers is essential for safety (Tick-induced Allergies Research and Awareness, n.d.-b).

Regarding mastocytosis, ASCIA advises that blood tests for mast cell tryptase may also be useful in diagnosing tick allergy (Australasian Society of Clinical Immunology and Allergy, 2019b). Tryptase is an enzyme that is increased in people with mastocytosis. It is associated with a higher risk of allergic reactions to many allergic triggers including insect stings and tick bites. People with higher tryptase levels may have more severe anaphylactic reactions to insect stings and bites (Australasian Society of Clinical Immunology and Allergy, 2019b).

Acute Adult Food Carbohydrate-Induced Enterocolitis Syndrome (FCIES)

TiARA advised the Health of Representatives Standing Committee on Health, Aged Care and Sport that FCIES, a novel entity described in 2019, comprised one of the tick-induced allergies (Tick-induced Allergies Research and Awareness, 2019).

The available information on acute adult FCIES comes from a short paper presented by TiARA to the ASCIA 2019 annual conference titled *Acute adult FCIES (food carbohydrate-induced enterocolitis syndrome) to mammalian meat after tick bite: a novel mechanism in mammalian meat reactivity* (Tick-induced Allergies Research and Awareness, n.d.-a). In this paper, the authors note that adult acute food protein-induced enterocolitis syndrome (FPIES) has been previously described, however, food induced enterocolitis had not been previously described to a carbohydrate antigen (acute FCIES). A retrospective survey of the clinical histories of 303 patients with symptoms after mammalian meat ingestion sought to identify clinical features. Three cases of adult tick-bitten patients with acute FCIES to mammalian

meat were identified and described in a presentation which is available on the TiARA website (Tick-induced Allergies Research and Awareness, n.d.-a).

The authors noted food-induced enterocolitis in response to a carbohydrate antigen is an uncommon cause of symptoms in those with mammalian meat reactivity (<1%; 3 out of 303). Diagnosis of FCIES, as for FPIES, relies upon typical clinical features; lack of specific IgE to putative antigen both supports the diagnosis and distinguishes it from IgE-mediated MMA (with its characteristic three to six hours delay to symptom onset) (Tick-induced Allergies Research and Awareness, n.d.-a).

More recently, in 2021, van Nunen and Ratchford provided the following advice on FCIES (van Nunen & Ratchford, 2021):

FCIES affects 1% of individuals who react to mammalian meat (Lauer et al. (2019) in van Nunen & Ratchford, 2021).

Patients with FCIES are convincingly negative for alpha-gal sIgE (as are patients who have FPIES); thus FCIES is not considered an IgE-mediated condition but is attributed to T cell-mediation.

The symptoms of FCIES are the same as those of FPIES and include:

protracted severe vomiting and diarrhoea

hypotension often occurs with this (severe vomiting and diarrhoea) due to a fluid phase shift in the gut

pallor and lethargy are typical features, in contrast to IgE-mediated reactions where erythema is usual.

For people who have FCIES, dietary advice is similar to that for people with mammalian meat anaphylaxis. The reintroduction of mammalian meat into the diet may be possible in future years provided there is no subsequent bite from a tick of any life stage; however, there is no *in vitro* test to guide the reintroduction of mammalian meat in people with FCIES and no current evidence specifically about the likely success and timing of this reintroduction (van Nunen & Ratchford, 2021).

Mild allergic reactions to tick bites

A local allergic reaction to ticks is not uncommon and may take the form of urticaria or induration (due to tick saliva), scrub itch (due to infestations of nymphs) or rash (Pearce & Grove (1987), Storer et al. (2005), and Doggett (2004) in Graves & Stenos, 2017).

Mild allergic reactions to ticks comprise large local reactions and appear as a large local swelling and inflammation at the site of the tick bite that may last for several days (Australasian Society of Clinical Immunology and Allergy, 2019b; Tick-induced Allergies Research and Awareness, n.d.-b).

Other mild or moderate reactions, which may not always occur before anaphylaxis, include swelling of lips, face, or eyes, hives or welts, or tingling mouth.

Large, local reactions to tick bites

Large local reactions to tick bites are the “least severe form” of tick-induced allergy (van Nunen, 2018; van Nunen & Ratchford, 2021). Mild allergic reactions to tick bites appear as a large local swelling and inflammation restricted to the site of the tick bite that typically extends from the bony joint above the bite to the bony joint below the bite, and can last for several days (Australasian Society of Clinical Immunology and Allergy, 2019b; Tick-induced Allergies Research and Awareness, n.d.-b; van Nunen, 2018; van Nunen & Ratchford, 2021).

Incidence

Precise statistics on the prevalence of allergic diseases overall are not available in Australia. Prevalence levels for allergic disease are generally collated from a range of National Health Surveys, Census data and hospital admissions data (Parliament of Australia, 2020). As such, the incidence of large, localised swellings attributed to tick bites in Australia is unknown.

An Australian study in 2013 that investigated the incidence of anaphylaxis in an e ED provides some insights into the presentation of allergic reactions after tick bite. In their retrospective analysis of patients presenting with tick bite at a large Australian ED on Sydney’s Northern Beaches over a two-year period from 1 January 2007 to 1 January 2009, the study found that, of the over 500 cases, 37% of patients (211 out of 566) were documented as having an allergic reaction to the tick (Rappo et al., 2013). Of these, 34 cases of anaphylaxis were recorded (6% or 34 out of 566), (Rappo et al., 2013), indicating that allergic reactions, other than anaphylaxis to the tick bite were more common presentations (31% or 177 out of 566).

Symptoms, clinical presentation and features

Mild allergic reactions to tick bites appear as a large local swelling and inflammation restricted to the site of the tick bite that typically extends from the bony joint above the bite to the bony joint below the bite, and can last for several days (Australasian Society of Clinical Immunology and Allergy, 2019b; Tick-induced Allergies Research and Awareness, n.d.-b; van Nunen, 2018; van Nunen & Ratchford, 2021). The large local reaction may present as a large area of induration (more than 5cm by 5cm) at the site of the tick bite (van Nunen & Ratchford, 2021). While the least dangerous type of allergic reaction to ticks, large local

reactions are physically limiting when present and very uncomfortable (Tick-induced Allergies Research and Awareness, n.d.-b; van Nunen, 2018; van Nunen & Ratchford, 2021).

The reactions commence within four to 12 hours of the tick bite, increase in size for 24 to 72 hours, reach their height by 72 hours and take seven to 10 days to resolve (Tick-induced Allergies Research and Awareness, n.d.-b; van Nunen, 2018; van Nunen & Ratchford, 2021). The swelling moves downwards due to gravity as the reactions resolve (van Nunen & Ratchford, 2021). Local reactions typically have no after effects (Tick-induced Allergies Research and Awareness, n.d.-b).

As seen with other insect bites and stings (Graft et al. (1984) in van Nunen, 2018), large local reactions to tick bites are due to late-phase allergic reaction primed by insect-specific IgG (Graft et al. (1984) in van Nunen, 2015, Gauci et al. (1989) in 2018).

Treatment

Large local reactions to tick bites are most effectively treated by:

- immobilisation of the affected area
- elevation of the affected area above the heart (if possible) to facilitate resolution of the intense oedema
- application of ice to the site of the tick bite, to help reduce pains and swelling
- administration of antihistamines, daily, commencing as soon as possible after the tick bite
- administration of oral corticosteroids, to suppress inflammation, taken immediately when large local reactions to tick bites have occurred (Tick-induced Allergies Research and Awareness, n.d.-b; van Nunen, 2015).

Large local reactions respond well to early administration of antihistamines and oral corticosteroids (van Nunen & Ratchford, 2021).

Large local reactions to tick bite are often indistinguishable from cellulitis, and patients may be treated with antibiotics, sometimes parenterally, particularly when the reaction affects the periorbital area (van Nunen & Ratchford, 2021). Patients should keep antihistamine and oral corticosteroid to hand, as early use after a subsequent tick bite may limit a subsequent reaction and reduce the possibility of requiring antibiotics (van Nunen & Ratchford, 2021).

The Australian Immunisation Handbook (https://immunisationhandbook.health.gov.au/) notes that bite wounds can lead to tetanus, however, ‘bite wounds’ are not intended to extend to tick bites. Therefore, clinicians do not need to check the tetanus immunisation status of patients who present with a tick bite.

See *Prevention and management of tick bites in Australia* Guidance Note for information on preventing tick bites and safely managing tick bites in Australia.

Tick-associated toxicosis and paralysis

Various forms of tick toxicosis affect humans and other animals and in their most severe form result in paralysis of the infested host (Hall-Mendelin et al., 2011). Globally, there are nearly 70 species of tick capable of inducing paralysis (Gothe & Neitz (1991) in Hall-Mendelin et al., 2011).

In Australia, tick paralysis has predominantly been seen as a problem in veterinary medicine with approximately 10,000 companion animals affected per year (Stone & Aylward (1987) in Hall-Mendelin et al., 2011). In Australia, the Australian paralysis tick, *I. holocyclus* is the most common tick that causes tick paralysis in domestic animals, humans and wildlife (Dehhaghi et al., 2019).

I. holocyclus can cause paralysis in humans, dogs, cats, sheep, cattle, goats, pigs and horses but predominantly infests dogs, cats, and humans (Stone (1986) in Hall-Mendelin et al., 2011).

To cause host paralysis, a tick must be attached for four to five days (Hall-Mendelin et al., 2011; Hall-Mendelin et al. (2011) in Taylor et al., 2019). Paralysis is induced by a toxin that is transmitted to the host in the saliva of a female *I. holocyclus*, when the tick takes a blood meal (Hall-Mendelin et al., 2011). The toxins produced by *I. holocyclus* inhibit acetylcholine release at the neuromuscular junction (Chand et al., 2016), and tend to cause more severe neurological impairment than the toxins from ticks in North America (Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011). Paralysis can extend even after the tick has been removed (Dehhaghi et al., 2019; Grattan-Smith et al. (1997) in Graves & Stenos, 2017).

Tick paralysis is rare in humans, as a tick must be attached for several days to inject enough toxin (Australasian Society of Clinical Immunology and Allergy, 2019b). Tick paralysis, while rare, is usually seen in children rather than adults (Australian Government Department of Health, 2015).

Tick paralysis caused by the Australian paralysis tick (*I. holocyclus*), while rarely severe, can be fatal (Hall-Mendelin et al., 2011). In Australia, between 1914 and 1942, 20 human fatalities were attributed to tick bite, with all but three fatalities being children (Murray & Koch (1969) in Hall-Mendelin et al., 2011). About 70% of these fatalities were in children under four years of age (Sutherland & Tibballs (2001) in Doggett, 2004). In Australia, there have not been human deaths due to tick paralysis, for many decades (since 1945) (Dehhaghi et al., 2019; Doggett, 2004; Grattan-Smith et al. (1997) in Graves & Stenos, 2017; Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011; Barker & Walker (2014) in Taylor et al., 2019) Deaths from the bite of *I. holocyclus* are now rare due to the addition of intensive care-units in regional hospitals and expert medical treatment [advances in intensive care treatment] (Barker & Barker, 2018), and an antivenene.

Ticks that can cause paralysis in Australia and internationally

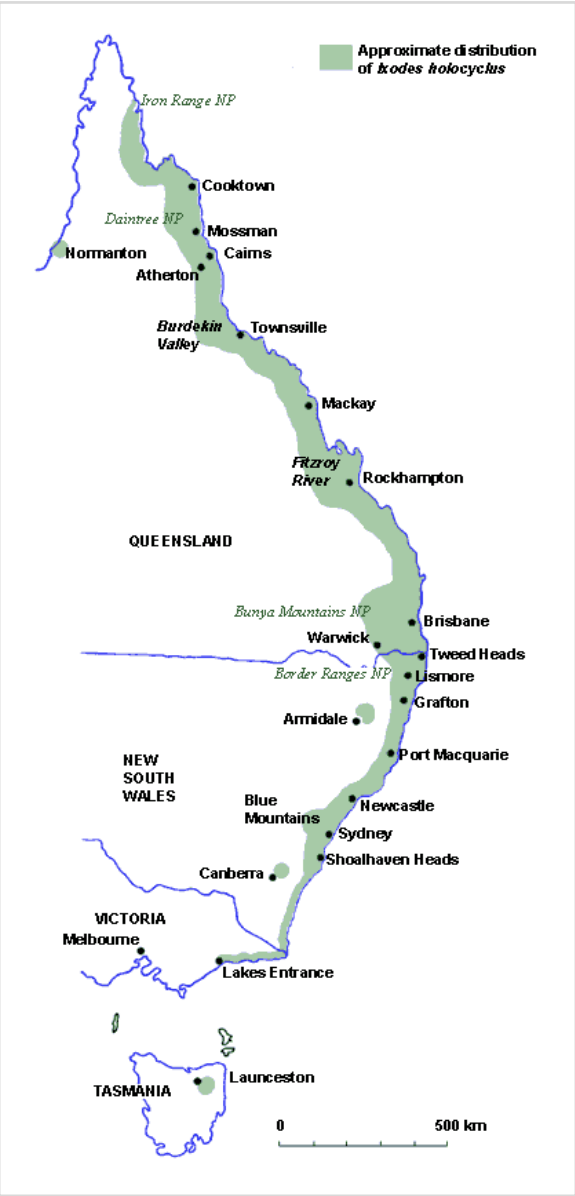
Nearly 70 species of ticks globally are capable of inducing paralysis (Gothe & Neitz (1991) in Hall-Mendelin et al., 2011). The important species of these ticks are found in:

- Australia: *I. holocyclus* (Australian paralysis tick)
- North America: *Dermacentor andersoni* (Rocky Mountain wood tick)*, Dermacentor variabilis* (American dog tick) and *Argas (Persicargas) radiatus* (fowl tick)
- South Africa: *Ixodes rubicundus* (Karoo paralysis tick)
- Ethiopia: *Rhipicephalus evertsi* (red-legged tick) and *Argas (Persicargas) walkerae* (fowl tampan tick)
- Neoartic region of North America: *Argas (Persicargas) radiatus* (fowl tick) (Stone (1986) in Hall-Mendelin et al., 2011).

The most important tick to cause paralysis is *I. holocyclus,* in Australia. The main distribution of the *I. holocyclus* tick (see Figure 2 overleaf) is within 20 km of the coast along virtually the entire eastern seaboard of Australia (Barker & Walker (2014), and Hardy et al. (2014) in Stewart et al., 2017a; Tick-induced Allergies Research and Awareness, n.d.-b). However, it has been isolated in areas more than 100 km inland including the Bunya Mountains, Barcaldine, and Thargomindah in Queensland and the Lower Blue Mountains in New South Wales (Stewart et al., 2017a; Tick-induced Allergies Research and Awareness, n.d.-b). It can also be found in the Australian Capital Territory, probably having travelled from the south coast on people and their companion animals (Tick-induced Allergies Research and Awareness, n.d.-b).

It is not known to occur in South Australia, Western Australia or the Northern Territory (Australian Government Department of Health, 2015).

Figure 2: Approximate geographic distribution of Australian paralysis tick (Ixodes holocyclus) (Public domain)



Public domain: Distribution map of the paralysis tick of Australia (Ixodes holocyclus)

Roberts FHS (1970) Australian Ticks. Yeerongpilly, Queensland.

Adapted from Roberts FHS (1970) Australian Ticks. Yeerongpilly, Queensland, by TAGS Inc, Bill Conroy & Norbert Fischer

https://en.wikipedia.org/wiki/File:Ixodes_holocyclus_distribution_map.png#/media/File:Ixodes_holocyclus_distribution_map.png

There are, however, two other *Ixodes* species in Australia that cause paralysis: the southern paralysis tick (*I. cornuatus*), which is found in Tasmania and Victoria, and Hirst's marsupial tick (*I. hirsti*), which is found in South Australia and has also been documented in New South Wales and Tasmania (Australian Government Department of Health, 2015).

The southern [Tasmanian] paralysis tick has been reported to cause bulbar paresis and respiratory failure in humans (Tibballs & Cooper (1986) in Hall-Mendelin et al., 2011) and dogs (Beveridge et al. (2004) in Hall-Mendelin et al., 2011). However, the habitat of *I. cornuatus* is more restricted than that of *I. holocyclus* and it has been associated with very few cases of paralysis (Hall-Mendelin et al., 2011).

Hirst's marsupial tick has kangaroos and their kin, domestic dogs and cats, and some birds as its hosts, not humans (Barker & Walker (2014) in Dehhaghi et al., 2019).

Incidence in Australia

Tick toxicosis in humans was first reported in 1884 by Bancroft, who described two cases with weakness and blurred vision (Bancroft (1884) in Hall-Mendelin et al., 2011). Tick paralysis is rare in humans as a tick must be attached for several days to inject enough toxin (Australasian Society of Clinical Immunology and Allergy, 2019b).

Tick paralysis occurs extensively in Australia with many researchers having reported human case studies, the geographical distribution of such cases being highly restricted to the enzootic range of the Australian paralysis tick (Dehhaghi et al., 2019).

Occasional cases of tick paralysis do still occur, mainly in children, with these rare cases often unrecognised or misdiagnosed (Doggett, 2004).

Demographics

Tick paralysis, while rare in humans, is usually seen in children rather than adults (Australian Government Department of Health, 2015). The most commonly affected group is children one to five years of age (Grattan Smith et al. (1997) in Dehhaghi et al., 2019; Grattan-Smith et al. (1997), and Inokuma et al. (2003) in Hall-Mendelin et al., 2011). The problem does however, also occur in older children and adults (Grattan-Smith et al. (1997), and Inokuma et al. (20013) in Hall-Mendelin et al., 2011).

Doggett noted that occasional cases of tick paralysis do still occur, mainly in children, with these rare cases often unrecognised or misdiagnosed (Doggett, 2004). Doggett noted that in a case at Westmead Hospital the cause of a mysterious coma in a young patient was found serendipitously when a nurse discovered the tick while stroking the child's head (Doggett, 2004).

There have been 20 documented fatalities due to tick paralysis and about 70% of these have been in children under four years of age (Sutherland & Tibballs (2001) in Doggett, 2004).

Toxicity of I. holocyclus saliva

When *I. holocyclus* bites, it injects a mixture of neurotoxins into its host. The toxins, known as holocyclotoxins, are small, cyclic polypeptides similar to botulinum toxin (Graves & Stenos, 2017). The toxins produced by *I. holocyclus* inhibits acetylcholine release at the neuromuscular junction (Chand et al., 2016) and tend to cause more severe neurological impairment than ticks in North America (Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011).

A single Australian paralysis tick (*I. holocyclus*) is capable of killing a large dog (Stone & Wright (1981) in Hall-Mendelin et al., 2011) or a sheep (Sloan (1968) in Hall-Mendelin et al., 2011). The role of these toxins for the tick is uncertain, but they often have a profound impact on the host animal and can affect native animals, family pets and occasionally humans, especially if the host is small (Grattan-Smith et al. (1997), and Miller (2002) in Graves & Stenos, 2017).

Paralysis is induced in the host by these toxins when transmitted in the saliva of a female *I. holocyclus* tick when the tick takes a blood meal. However, paralysis is not instantaneous. Hall-Mendelin et al. noted the interesting clinical phenomenon of *I. holocyclus* is that this tick needs several days of engorgement on their host before signs of paralysis manifest (Hall-

Mendelin et al., 2011). During feeding, toxicity in the salivary glands of *I. holocylcus* increases, peaking after four to five days of engorgement (Goodrich & Murray (1978) in Hall-Mendelin et al., 2011).

The Australian paralysis tick appears to be the most potently toxic tick species globally (Hall-Mendelin et al., 2011). Tick paralysis caused by the *I. holocyclus,* while rarely severe, can be fatal (Hall-Mendelin et al., 2011). In Australia, between 1914 and 1942, 20 human fatalities were attributed to tick bite, with all but three fatalities being children (Murray & Koch (1969) in Hall-Mendelin et al., 2011). Paralysis caused by the holocyclotoxin in the saliva of *I. holocyclus* has resulted in higher human mortality than either red-back or funnel-web spiders (Sutherland & Tibballs (2001) in Barker & Barker, 2018; Nicholson et al. (2006), and Miller (2002) in Taylor et al., 2019)

While *I. holocyclus* ticks generally appear to be consistently toxic, Hall-Mendelin et al. noted there is some evidence of variation in toxin potency in this species (Alexander (1986), Curtin (1986), Jones (1986), Pursell (1986), and Atwell & Fitzgerald (1994) in Hall-Mendelin et al., 2011).

Physiological reaction of the host to I. holocyclus tick toxin

Motor paralysis induced by the toxin of *I. holocyclus* occurs as a result of action at the host's neuromuscular junctions (Chand et al., 2016; Cooper & Spence (1976) in Hall-Mendelin et al., 2011). In humans and other animals affected by holocyclotoxin from *I. holocyclus,* Hall-Mendelin et al. noted the cortex of the central nervous system seems generally unaffected, as cases remain alert and conscious and sensations are retained (Stone (1986) in Hall-Mendelin et al., 2011). Research has shown that the *I. holocyclus* salivary toxin directly affects vascular and cardiac potassium channels by blockade, with this action differing from the respiratory distress caused by progressive muscle paralysis (Atwell et al. (2001) in Hall-Mendelin et al., 2011).

Hall-Mendelin et al. noted it is not known if the limb paralysis and cardiovascular changes seen in mammals bitten by *I. holocyclus* are elicited by one or more separate toxins (Hall-Mendelin et al., 2011).

Symptoms

Early symptoms

Early symptoms of tick paralysis may include:

- rashes, headache, fever, influenza-like symptoms, tenderness of lymph nodes, unsteady gait, intolerance to bright light, increasing weakness of the limbs, and partial facial paralysis (Australian Government Department of Health, 2015; Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011)
- loss of appetite and slurred speech (Grattan-Smith et al. (1997), and Edlow & McGillicuddy (2008) in Hall-Mendelin et al., 2011)
- children becoming subdued, refusing food, and sleeping for excessive periods (Grattan Smith et al. (1997) in Dehhaghi et al., 2019)
- difficulty in reading due to double vision [as a result of eye muscle weakness], nystagmus [repetitive uncontrollable eye movements], or photophobia in older children and adults (Sutherland & Tibballs (2001), and Barker & Walker (2014) in Dehhaghi et al., 2019)

- laboured breathing (Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011).

Over 24 hours the paralysis will continue to involve the arms and the muscles involved in swallowing (Doggett, 2004).

Clinical features and presentation of tick paralysis

To cause host paralysis, a tick must be attached for four to five days (Hall-Mendelin et al., 2011; Hall-Mendelin et al. (2011) in Taylor et al., 2019). The most commonly affected group is children one to five years of age (Grattan Smith et al. (1997) in Dehhaghi et al., 2019).

From combined evidence (presented below this list), clinical presentation of tick paralysis can involve a combination of the following:

- Lethargy
- Weakness and unsteadiness of gait, often with ataxia
- Loss of appetite
- Dilated pupils
- Double or blurred vision may develop in older children or adults
- Ascending symmetrical flaccid paralysis
- Slurred speech
- Depressed deep-tendon and gag reflexes
- Laboured breathing
- Bradycardia
- Decreased oxygen saturation and asystole
- Myocarditis in children.

The toxins of *I. holocyclus* may cause ataxia followed by an ascending, symmetrical, flaccid paralysis similar to Guillain-Barré syndrome. Cranial nerves may be involved, leading to facial paralysis or ophthalmoplegia (Grattan-Smith (1997) in Dehhaghi et al., 2019; Graves & Stenos, 2017; Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011). Hall-Mendellin et al. provided a more extensive description of the clinical presentation of tick paralysis. They advised the clinical presentation of tick paralysis usually involves a combination of lethargy, weakness and unsteadiness of gait, often with ataxia, loss of appetite, dilated pupils, ascending symmetrical paralysis, slurred speech and depressed deep-tendon and gag reflexes (Grattan-Smith et al. (1997), and Edlow & McGillicuddy (2008) in Hall-Mendelin et al., 2011). Laboured breathing, bradycardia, decreased oxygen saturation and asystole have also been reported (Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011).

In children, the toxin from *I. holocyclus* can also cause myocarditis, in addition to neuromuscular paralysis (Pearn (1966) in Hall-Mendelin et al., 2011).

Double or blurred vision may develop in older children or adults (Grattan-Smith et al. (1997), and Edlow & McGillicuddy (2008) in Hall-Mendelin et al., 2011).

Over 24 hours the paralysis will continue to involve the arms and the muscles involved in swallowing; the patient may possibly require artificial ventilation (Doggett, 2004). Fatalities in the past have been due to respiratory failure (Doggett, 2004).

Hall-Mendelin et al. noted that facial weakness or paralysis may be present and ascending flaccid paralysis may also occur if the tick is not removed “quickly”(Pearn (1977) in Hall-

Mendelin et al., 2011). However, they also noted that removal of *I. holocyclus* from a patient can worsen the patient's condition, with tick removal apparently leading to deterioration in four of the six cases Grattan-Smith et al. had described (Hall-Mendelin et al., 2011). Such delayed toxicity was hypothesised by Stone et al. to be caused by the disruption of the feeding lesion during removal of the tick which causes the release of toxin that had been bound to cells or tissues (Stone et al. (1989) in Hall-Mendelin et al., 2011).

Paralysis can extend even after the tick has been removed (Dehhaghi et al., 2019; Grattan-Smith et al. (1997) in Graves & Stenos, 2017). The progress of paralysis continues for 24 to 48 hours after removal of *I. holocyclus*, in contrast to the short duration seen with North American ticks (Dehhaghi et al., 2019).

It is crucial to carefully observe an affected patient during this period. If the affected patient's condition worsens during this period seek medical attention quickly. There has not been a death from tick paralysis in Australia since 1945 but it can be fatal if left untreated. See section on 'Treatment' for more detail.

Dehhaghi et al. noted that according to reports (by Sutherland & Tibballs (2001) and Barker & Walker (2014)) there is no increase in body temperature during tick paralysis unless the disease is complicated by bacterial infection (Dehhaghi et al., 2019).

Differential diagnosis in tick paralysis

Guillain-Barré syndrome (GBS) may be commonly confused with tick paralysis (Hall-Mendelin et al., 2011). Other conditions and diseases that may need to be considered in a differential diagnosis are:

- viral encephalomyelitis
- botulism
- myasthenia gravis
- spinal-cord compression
- transverse myelitis
- organo-phosphate poisoning
- porphyria
- heavy-metal poisoning
- diphtheria (Hall-Mendelin et al., 2011).

Hall-Mendelin et al. provided a table on the factors to be considered in the differential diagnosis of tick paralysis. See Table 2 in Hall-Mendelin et al. (2011) for further information.

Fatalities from tick paralysis

Tick paralysis caused by the Australian paralysis tick (*I. holocyclus*), while rarely severe, can be fatal (Hall-Mendelin et al., 2011). In Australia, between 1914 and 1942, 20 human fatalities were attributed to tick bite, with all but three fatalities being children (Murray & Koch (1969) in Hall-Mendelin et al., 2011). About 70% of these fatalities were in children under four years of age (Sutherland & Tibballs (2001) in Doggett, 2004). In all of these cases, when known, the site of tick attachment was on the chest or higher, with the vast majority of attachment sites being on the head (Doggett, 2004).

In Australia, there have not been human deaths due to tick paralysis for many decades (since 1945) (Dehhaghi et al., 2019; Doggett, 2004; Grattan-Smith et al. (1997) in Graves & Stenos, 2017; Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011; Barker & Walker (2014) in Taylor et al., 2019) and deaths from the bite of *I. holocyclus* are now rare due to the addition of intensive care-units in regional hospitals and expert medical treatment [advances in intensive care treatment] (Barker & Barker, 2018), and an antivenene.

Treatment

Untreated tick paralysis can be fatal in humans (Hall-Mendelin et al., 2011). Hall-Mendelin noted the following regarding treatment of tick paralysis:

- Locating and removing all ticks from the patient's body is an important part of therapy, despite the risk of a short-term worsening in the patient's symptoms (Edlow & McGillicuddy (2008) in Hall-Mendelin et al., 2011).
- While ticks are found most commonly on the scalp and behind the ear, a thorough investigation of the patient's body may be warranted.
- While tick antitoxin is available, the heterologous nature of the antiserum can induce serum sickness and anaphylactic shock in humans (Stone et al. (1982) in Hall-Mendelin et al., 2011).
- Progression of paralysis may require mechanical respiratory ventilation in an intensive care unit (Grattan-Smith et al. (1997) in Hall-Mendelin et al., 2011).
- The [possible] administration of antibiotics to protect against *Rickettsia* and *Orientia* (Inokuma et al. (2003) in Hall-Mendelin et al., 2011).

A full recovery is usually slow and may take several weeks (Doggett, 2004).

The Australian Immunisation Handbook (https://immunisationhandbook.health.gov.au/) notes that bite wounds can lead to tetanus, however, 'bite wounds' are not intended to extend to tick bites. Therefore, clinicians do not need to check the tetanus immunisation status of patients who present with a tick bite.

See *Prevention and management of tick bites in Australia* Guidance Note for information on preventing tick bites and safely managing tick bites in Australia.

References

Australasian Society of Clinical Immunology and Allergy. (2019a). *Information for patients, consumers and carers*. Australasian Society of Clinical Immunology and Allergy. https://www.allergy.org.au/images/pcc/ASCIA_PCC_Tick_Allergy_2019.pdf

Australasian Society of Clinical Immunology and Allergy. (2019b). *Tick allergy*. Australasian Society of Clinical Immunology and Allergy. https://www.allergy.org.au/ticks

Australasian Society of Clinical Immunology and Allergy. (2020). *ASCIA guidelines: Acute management of anaphylaxis in pregnancy 2020*. Australasian Society of Clinical Immunology and Allergy. https://www.allergy.org.au/hp/papers/acute-management-of-anaphylaxis-in-pregnancy

Australasian Society of Clinical Immunology and Allergy. (2021a). *ASCIA Guidelines—Acute management of anaphylaxis*. Australasian Society of Clinical Immunology and Allergy. https://www.allergy.org.au/hp/papers/acute-management-of-anaphylaxis-guidelines

Australasian Society of Clinical Immunology and Allergy. (2021b, February 23). *Anaphylaxis resources*. Australasian Society of Clinical Immunology and Allergy. https://www.allergy.org.au/anaphylaxis

Australasian Society of Clinical Immunology and Allergy. (2022). *Allergy, immunodeficiency, autoimmunity and COVID-19 vaccination frequently asked questions (FAQ)*. Australasian Society of Clinical Immunology and Allergy. https://www.allergy.org.au/patients/ascia-covid-19-vaccination-faq

Australian Government Department of Health. (2015, November 25). *Tick bite prevention*. https://www1.health.gov.au/internet/main/publishing.nsf/Content/ohp-tick-bite-prevention.htm

Australian Government Department of Health. (2020). *Debilitating Symptom Complexes Attributed to Ticks (DSCATT) Clinical Pathway*. https://www1.health.gov.au/internet/main/publishing.nsf/Content/4594AB5B9B2A90D4CA257BF0001A8D43/$File/Clinical-Pathway.pdf

Barker, S. C., & Barker, D. (2018). Ticks in Australia: Endemic; exotics, which ticks bite humans? *Microbiology Australia*, *39*(4), 194–199. https://doi.org/10.1071/MA18062

Centers for Disease Control and Prevention. (2020, October 6). *Alpha-gal syndrome*. Centers for Disease Control and Prevention. https://www.cdc.gov/ticks/alpha-gal/index.html

Chand, K. K., Lee, K. M., Lavidis, N. A., Rodriguez-Valle, M., Ijaz, H., Koehbach, J., Clark, R. J., Lew-Tabor, A., & Noakes, P. G. (2016). Tick holocyclotoxins trigger host paralysis by presynaptic inhibition. *Scientific Reports*, *6*(1), 1–4. https://doi.org/10.1038/srep29446

Dehhaghi, M., Panahi, H. K. S., Holmes, E. C., Hudson, B. J., Schloeffel, R., & Guillemin, G. J. (2019). Human tick-borne diseases in Australia. *Frontiers in Cellular and Infection Microbiology*, *9*, 1–17. https://doi.org/10.3389/fcimb.2019.00003

Doggett, S. L. (2004). Ticks: Human health and tick bite prevention. *Medicine Today*, *5*(11), 33–38.

Geary, M. J., Russell, R. C., Moerkerken, L., Hassan, A., & Doggett, S. L. (2021). 30 years of samples submitted to an Australian Medical Entomology Department. *Austral Entomology*, *60*(1), 172–197. https://doi.org/10.1111/aen.12480

Graves, S. R., & Stenos, J. (2017). Tick-borne infectious diseases in Australia. *Medical Journal of Australia*, *206*(7), 320–324. https://doi.org/10.5694/mja17.00090

Hall-Mendelin, S., Craig, S. B., Hall, R. A., O'Donoghue, P., Atwell, R. B., Tulsiani, S. M., & Graham, G. C. (2011). Tick paralysis in Australia caused by *Ixodes holocyclus* Neumann. *Annals of Tropical Medicine and Parasitology*, *105*(2), 95–106. https://doi.org/10.1179/136485911X12899838413628

Kaneko, Y., Kitano, S., Umayahara, T., Kageyama, R., & Hashizume, H. (2019). Tick anaphylaxis in Japan. *Journal of Cutaneous Immunology and Allergy*, *2*(2), 53–54. https://doi.org/10.1002/cia2.12046

Kwak, M. L., Somerville, C., & van Nunen, S. A. (2018). A novel Australian tick *Ixodes (Endopalpiger) australiensis* inducing mammalian meat allergy after tick bite. *Asia Pacific Allergy*, *8*(3), 1–4. https://doi.org/10.5415/apallergy.2018.8.e31

Lydecker, H., Stanfield, E., Lo, N., Hochuli, D., & Banks, P. (2014). Are urban bandicoots solely to blame for tick concerns? *Australian Zoologist*, *37*(3), 288–293. https://doi.org/10.7882/AZ.2015.008

McGain, F., Welton, R., Solley, G. O., & Winkel, K. D. (2016). First fatalities from tick bite anaphylaxis. *Journal of Allergy and Clinical Immunology: In Practice*, *4*(4), 769–770. https://doi.org/10.1016/j.jaip.2015.12.023

Mullins, R. J., Wainstein, B. K., Barnes, E. H., Liew, W. K., & Campbell, D. E. (2016). Increases in anaphylaxis fatalities in Australia from 1997 to 2013. *Clinical and Experimental Allergy*, *46*(8), 1099–1110. https://doi.org/10.1111/cea.12748

Parliament of Australia. (2020). *Walking the allergy tightrope*. House of Representatives Standing Committee on Health, Aged Care and Sport. https://parlinfo.aph.gov.au/parlInfo/download/committees/reportrep/024422/toc_pdf/Walkingtheallergytightrope.pdf;fileType=application%2Fpdf

Pattarabanjird, T., Wilson, J. M., Erickson, L. D., Workman, L. J., Qiao, H., Ghosheh, Y., Gulati, R., Durant, C., Vallejo, J., Saigusa, R., Platts-Mills, T. A. E., Taylor, A. M., Ley, K., & McNamara, C. A. (2022). Chemokine receptor activation enhances memory B cell class switching linked to IgE sensitization to alpha gal and cardiovascular disease. *Frontiers in Cardiovascular Medicine*, *8*. https://doi.org/10.3389/fcvm.2021.791028

Rappo, T. B., Cottee, A. M., Ratchford, A. M., & Burns, B. J. (2013). Tick bite anaphylaxis: Incidence and management in an Australian emergency department. *Emergency Medicine Australasia*, *25*(4), 297–301. https://doi.org/10.1111/1742-6723.12093

Schmidle, P., Mehlich, J., Brockow, K., Darsow, U., Biedermann, T., & Eberlein, B. (2021). Gelatin-containing vaccines for varicella, zoster, measles, mumps, and rubella induce basophil activation in patients with alpha-gal syndrome. *International Archives of Allergy and Immunology*, *182*, 716–722. https://doi.org/10.1159/000514263

Šimo, L., Kazimirova, M., Richardson, J., & Bonnet, S. I. (2017). The essential role of tick salivary glands and saliva in tick feeding and pathogen transmission. *Frontiers in Cellular and Infection Microbiology*, *7*(281), 1–23. https://doi.org/10.3389/fcimb.2017.00281

Stewart, A., Armstrong, M., Graves, S. R., & Hajkowicz, K. (2017a). *Rickettsia australis* and Queensland Tick Typhus: A Rickettsial Spotted Fever Group Infection in Australia. *American Journal of Tropical Medicine and Hygiene*, *97*(1), 24–29. https://doi.org/10.4269/ajtmh.16-0915

Sukkanon, C., Chareonviriyaphap, T., & Doggett, S. L. (2019). Topical and spatial repellent bioassays against the Australian paralysis tick, *Ixodes holocyclus* (Acari: Ixodidae). *Austral Entomology*, *58*(4), 866–874. https://doi.org/10.1111/aen.12420

Taylor, B. W. P., Ratchford, A., van Nunen, S. A., & Burns, B. (2019). Tick killing *in situ* before removal to prevent allergic and anaphylactic reactions in humans: A cross-sectional study. *Asia Pacific Allergy*, *9*(2), 1–13. https://doi.org/10.5415/apallergy.2019.9.e15

Taylor, C. L., Lydecker, H. W., Lo, N., Hochuli, D. F., & Banks, P. B. (2020). Invasive rabbits host immature *Ixodes* ticks at the urban-forest interface. *Ticks and Tick-Borne Diseases*, *11*(4), 1–7. https://doi.org/10.1016/j.ttbdis.2020.101439

Tick-induced Allergies Research and Awareness. (n.d.-a). Acute adult FCIES. Tick-Induced Allergies Research and Awareness. https://www.tiara.org.au/acute-adult-fcies-food-carbohydrate-induced-enterocolitis-syndrome-to-mammalian-meat-after-tick-bite-a-novel-mechanism-in-mammalian-meat-reactivity

Tick-induced Allergies Research and Awareness. (n.d.-b). *Tick anaphylaxis and mammalian meat allergy resources*. Tick-Induced Allergies Research and Awareness. https://www.tiara.org.au/tick-anaphylaxis-mammalian-meat-allergy-resources

Tick-induced Allergies Research and Awareness. (2019). *TiARA submission to the Inquiry into allergies and anaphylaxis*. Parliament of Australia.

https://www.aph.gov.au/DocumentStore.ashx?id=7ada1cba-a279-47a0-b80e-c2f8521005b4&subId=671917

van Nunen, S. A. (2015). Tick-induced allergies: Mammalian meat allergy, tick anaphylaxis and their significance. *Asia Pacific Allergy*, *5*(1), 3–16. https://doi.org/10.5415/apallergy.2015.5.1.3

van Nunen, S. A. (2018). Tick-induced allergies: Mammalian meat allergy and tick anaphylaxis. *Medical Journal of Australia*, *208*(7), 316–321. https://doi.org/10.5694/mja17.00591

van Nunen, S. A., & Ratchford, A. (2021). Managing mammalian meat allergy and tick anaphylaxis. *Medicine Today*, *22*(3), 22–32.

Vernon, S. T., Kott, K. A., Hansen, T., Finemore, M., Baumgart, K. W., Bhindi, R., Yang, J., Hansen, P. S., Nicholls, S. J., Celermajer, D. S., Ward, M. R., van Nunen, S. A., Grieve, S. M., & Figtree, G. A. (2022). Immunoglobulin E sensitization to Mammalian Oligosaccharide Galactose-α-1,3 (α-Gal) is associated with noncalcified plaque, obstructive coronary artery disease, and ST-segment–elevated myocardial infarction. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *42*, 352–361. https://doi.org/10.1161/ATVBAHA.121.316878