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FOREWORD FROM THE SUPPLEMENT EDITOR

The prevalence of many allergic disorders continues to increase, with allergies among the most common presenting problems in general practice. This Anaphylaxis Supplement presents a collection of papers outlining important aspects of diagnosis and management of common allergic conditions.

Anaphylaxis is a severe, potentially life-threatening allergic reaction most commonly caused by foods, medications and venom. Life-saving first aid treatment is available via two adrenaline autoinjector devices. When and how to administer requires careful explanation and training.

Food allergy among children continues to be a major concern, with one in 10 infants in Australia diagnosed with an IgE-mediated food allergy and peanut allergy has increased 100% in last 10 yrs. Correct diagnosis and anaphylaxis education are essential components of management.

Venom-induced anaphylaxis is an important cause of mortality, particularly among middle-aged males. Unfortunately, many of those who died following a sting had experienced a previous venom-induced anaphylaxis. When to recommend referral for venom immunotherapy is an important consideration in general practice.

We hope you find these articles informative and helpful in assisting in managing patients with allergic disorders.

Connie H. Katelaris MB BS, PhD, FRACP
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KATIE FRITH MB BS, FRACP, MRCPCH
PREETI JOSHI MB BS, FRACP, PhD

Anaphylaxis is occurring more frequently in Australia and the rate of fatal reactions is increasing. Prompt recognition and early treatment with intramuscular adrenaline can reduce the risk of death.

Anaphylaxis is a potentially life-threatening allergic reaction that can present at any age. Anaphylactic reactions are unpredictable and initial signs of fatal anaphylaxis can be mild.[1-4] Allergic reactions defined as anaphylaxis are those that are potentially life threatening and require early treatment with adrenaline to reduce the risk of death.[4] Common causes of anaphylaxis include foods, medications and insect venom, but rare causes such as exercise or cold temperatures need to be considered. Although anaphylaxis often has a rapid onset, certain triggers may cause anaphylaxis several hours after allergen exposure, for example galactose-alpha-1,3-galactose (alpha-gal allergy, mammalian meat allergy).[5]

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KEY POINTS

- Anaphylaxis is a potentially life-threatening allergic reaction that can affect people of any age, including infants.
- Anaphylactic reactions can be unpredictable and may initially present with mild symptoms.
- Rates of hospital admission for anaphylaxis and fatalities from anaphylaxis are increasing in Australia.
- Adrenaline is the first-line treatment for anaphylaxis and should be given without delay by intramuscular injection into the outer mid-thigh; there are no contraindications for adrenaline in the management of anaphylaxis.
- Correct positioning of a patient with anaphylaxis is essential, as an upright posture is a risk factor for fatal reactions.
- Adrenaline injectors (AIs) allow easy, prompt administration of adrenaline and are designed to be used by people without medical training. There are two AI devices available in Australia on the PBS.
- The Australasian Society of Clinical Immunology and Allergy (ASCIA) now recommends a 150 mcg AI can be prescribed for infants weighing from 7.5 to 20 kg; children weighing 20 kg or more should be prescribed a 300 mcg AI, and from around 12 years (if weight greater than 50 kg) either a 300 mcg or 500 mcg AI is recommended.
- ASCIA has recently updated its guidelines for the acute management of anaphylaxis and has also updated its e-learning courses and anaphylaxis resources in line with current evidence.

The rate of anaphylaxis from all causes is increasing in Australia, with anaphylaxis due to foods increasing most. Prompt administration of intramuscular adrenaline is safe and should be first-line treatment for anaphylaxis. Antihistamines and corticosteroids do not treat or prevent anaphylaxis and should not be given before adrenaline. Appropriate management of patients with anaphylaxis includes ensuring they have adequate education about their triggers, how to avoid their allergen and how to recognise and treat anaphylaxis. Some online resources for doctors and patients are recommended in the Box. The Australasian Society of Clinical Immunology and Allergy (ASCIA) has recently updated its guidelines for health professionals for the acute management of anaphylaxis in line with current evidence.

Presentation and diagnosis

The diagnosis of anaphylaxis is made clinically, thus it is imperative that symptoms and signs are recognised promptly. Definitions of anaphylaxis vary worldwide but ASCIA defines anaphylaxis as:

- 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; or
- any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.[6]

ASCIA's definition of anaphylaxis is consistent with criteria recently published in the World Allergy Organization's anaphylaxis guidance 2020 position paper, which is now included in the updated ASCIA guideline.[4] There are controversies regarding some definitions of anaphylaxis. Certain classifications of anaphylaxis require more than one system to be involved, for example skin and respiratory and/or gastrointestinal system involvement; however, some fatal anaphylactic reactions may present with severe involvement of the respiratory or cardiovascular system alone.[4]

Confusion also arises with how to classify gastrointestinal symptoms such as abdominal pain or vomiting in allergic reactions. Gastrointestinal symptoms of any severity are considered signs of anaphylaxis in allergic reactions to insect stings or injected drugs; however, vomiting and abdominal pain may occur commonly in mild to moderate allergic reactions to foods. Severe, persistent gastrointestinal symptoms may be a feature of anaphylaxis from any cause.[6,7] The severity of gastrointestinal symptoms is based on clinical assessment, and if severe they usually respond well to intramuscular (IM) adrenaline.

Respiratory symptoms are more common in paediatric cases of anaphylaxis, and cardiovascular involvement occurs more commonly in adults.[8] Anaphylactic reactions may be underrecognised, as up to 20% of reactions occur without cutaneous involvement.[4,8] Anaphylaxis may also present solely with subjective symptoms, such as throat tightness, which may not be perceived to be severe.[8]

Serum tryptase level may be elevated a few hours after anaphylaxis compared with a patient's baseline and may assist in confirming a diagnosis of anaphylaxis if there is uncertainty or symptoms are atypical.[3] Treatment should not be delayed while waiting for tryptase results if anaphylaxis is suspected (Table 1).

Infants

Anaphylaxis can be difficult to recognise in infants, who cannot verbalise their symptoms and may present with nonspecific signs such as irritability, drooling and sleepiness.[9] A high index of suspicion is required as, although uncommon in this age group, fatalities have occurred.[10] Tachycardia, which may signal hypotension, can be a sign of anaphylaxis in infants but needs to be interpreted carefully and in context, as other causes of tachycardia may include crying, fever or pain.[9] Cardiovascular collapse is rare in infants with anaphylaxis and hypotension is a late sign in infants due to high peripheral vascular resistance and may represent a prearrest sign.[9]

Pregnancy

Anaphylaxis in pregnancy is rare, with most cases occurring in the intrapartum and postpartum period.[11] Common triggers include antibiotics, latex and anaesthetic agents; however, foods and insect venom also need to be considered. In addition to the usual signs and symptoms, anaphylaxis presentation in pregnancy may also include uterine cramps, persistent low blood pressure, lower back pain and fetal distress.[11]

ASCIA recently published guidelines on the acute management of anaphylaxis in pregnancy.[12] Management is similar to

ANAPHYLAXIS AND ALLERGY RESOURCES

- **ASCIA**, the peak professional body for clinical immunology/allergy specialists in Australia and New Zealand, offers a wide range of up-to-date evidence-based allergy resources, including medication-specific action plans for management of anaphylaxis (https://www.allergy.org.au/hp/anaphylaxis/)
- **Allergy and Anaphylaxis Australia**, a registered charity and Australia's only national support organisation dedicated to helping individuals and carers alike in managing allergy and the risk of anaphylaxis, offers an extensive range of online resources and support (https://allergyfacts.org.au/)
- **250K** is a hub for young Australians living with severe allergy (https://250k.org.au/)
- **Nip Allergies in the Bub** is a food-allergy prevention project (https://preventallergies.org.au/)

TABLE 1. SIGNS AND SYMPTOMS OF ALLERGIC REACTIONS[6]

Severity of reaction	Signs and symptoms
Mild to moderate reaction	• Cutaneous: urticaria, angioedema • Gastrointestinal: abdominal pain, vomiting*
Severe reaction (anaphylaxis)	• Respiratory: wheeze, persistent cough, stridor, chest tightness, difficulty breathing, difficulty swallowing, vocal changes (hoarse voice) • Cardiovascular: dizziness, collapse, pallor, floppiness/lethargy (young children)

* These are signs of anaphylaxis for insect allergy or injected drug allergy.

that for nonpregnant patients. Adrenaline is the cornerstone of anaphylaxis management in pregnant patients and should not be delayed due to concerns of causing reduced placental perfusion, as benefits of maintaining maternal blood pressure outweigh potential risks.[11] The same dose of adrenaline is recommended in pregnant patients (adrenaline [1:1000] 0.01 mg/kg IM). An adrenaline injector (AI) 300 mcg or 500 mcg is a reasonable option to reduce delay in administration if available.

Epidemiology

In Australia, the rate of hospital presentation for anaphylaxis from any cause is increasing. The greatest increase is seen in anaphylaxis to foods, at 10% per year in all age groups between 1997 and 2013, with the most significant rise occurring in older children and adolescents.[1]

Anaphylaxis fatalities are higher in Australia compared with other countries, and the cause of this is unclear. Anaphylaxis fatalities have been increasing at a rate of 6% per year, with food anaphylaxis deaths increasing at the greatest rate.[1] Deaths most commonly occurred due to reactions to medications and stinging insects in men aged over 50 years with comorbidities. Risk factors for fatal anaphylaxis include upright posture after anaphylaxis, delayed administration of adrenaline (epinephrine), concomitant asthma and delayed initiation of cardiopulmonary rescuscitation after collapse.[1,13]

TABLE 2. ANAPHYLAXIS TRIGGERS

Category	Common triggers	Less common triggers
Foods	• Peanut • Tree nuts • Seafood • Cow's milk • Egg • Wheat • Sesame • Soy	• Other foods e.g. fruits, vegetables
Drugs	• Antibiotics • NSAIDs	• Biological medications – transfusions – monoclonal antibodies – immunoglobulin
Stings and bites	• Honeybee • Wasps • Ants	• Ticks
Physical	–	• Exercise (with or without food) • Cold
Other	–	• Latex • Contrast media • Topical medicines e.g. betadine, chlorhexidine

Triggers

Common causes of anaphylaxis include foods, insect stings and medications (Table 2). Anaphylaxis may also be caused by physical triggers such as exercise or cold exposure. Up to 30% of anaphylaxis cases may be idiopathic, although this is a diagnosis of exclusion and may occur in patients with anaphylaxis to known causes.[14] In Australia, hospital admissions for anaphylaxis from all causes are increasing in line with similar trends observed in the US and UK.[1,13] In children, food triggers are the most common cause of anaphylaxis, and reactions to peanut, tree nuts, cow's milk, egg and seafood are responsible for most presentations.[15]

In food allergy, anaphylaxis usually occurs within one to two hours of ingestion of the allergen, and the onset may be rapid, often within 30 minutes. Mammalian meat anaphylaxis and food-dependent exercise-induced anaphylaxis are examples of conditions in which symptoms may be delayed several hours after ingesting a food allergen.[5,8] Anaphylaxis to animal stings and injected medications, including radiocontrast agents and

vaccines, usually occurs within five to 30 minutes but may be delayed.[8]

The presence of cofactors such as exercise, fever, hormonal status and acute infection may increase the likelihood of an allergic reaction or its severity.[8] Alcohol and NSAIDs may potentiate some allergic reactions to foods as well as reduce a person's capacity to recognise and manage their reaction.[1,8] True biphasic reactions are estimated to occur in 3 to 20% of patients at a median of 11 hours after the initial reaction (range 0.5 to 72 hours).[3,16]

Management

Adrenaline

Adrenaline (epinephrine) is the first-line drug of choice for the acute management of anaphylaxis and should be administered early.[3,6,8] There are no contraindications to the administration of IM adrenaline in the treatment of anaphylaxis.[8] Adrenaline acts to reduce airway mucosal oedema, induce bronchodilation, induce vasoconstriction and increase cardiac contraction strength.[3,8] ASCIA recommends IM adrenaline (1:1000) 0.01 mg/kg, up to a maximum of 0.5 mg, should be administered without delay into the outer mid-thigh if signs of anaphylaxis are present (Table 3).

IM adrenaline should be administered early via an adrenaline injector or needle and syringe if there are signs of anaphylaxis. Further doses of IM adrenaline can be given after five minutes if symptoms of anaphylaxis persist or recur.[6,8] Owing to an increased risk of adverse effects, boluses of intravenous (IV) adrenaline are not recommended as a first-line treatment for anaphylaxis outside of the operating theatre.[3,17,18] Similarly, subcutaneous adrenaline is not recommended, as absorption is not as reliable as IM administration.[3,8,19]

If symptoms of anaphylaxis persist despite two or more doses of IM adrenaline, an IV infusion of adrenaline can be considered if a health professional with the required skills and equipment is available.[3,6,8,20] Cardiopulmonary resuscitation (CPR) should be commenced if despite adrenaline administration the patient is unresponsive and not breathing effectively.[1,6,8]

TABLE 3. ASCIA-RECOMMENDED ADRENALINE DOSES FOR MANAGING ANAPHYLAXIS[6]

Approximate age (years)	Weight (kg)	Volume of adrenaline 1:1000	Appropriate adrenaline injector*
<1	<7.5	0.1 mL	Not available
1 to 2	10	0.1 mL	150 mcg device for children 7.5 to 20 kg (up to about 5 years)
2 to 3	15	0.15 mL	
4 to 6	20	0.2 mL	
7 to 10	30	0.3 mL	300 mcg device for children 20 to 50 kg (about 5 to 12 years)
10 to 12	40	0.4 mL	
≥12	>50	0.5 mL	300 mcg or 500 mcg devices for anyone over 50 kg

Abbreviations: AI = adrenaline injector; ASCIA = Australasian Society of Clinical Immunology and Allergy.
* Two brands of AI are available in Australia on the PBS (as well as a generic Mylan AI that is identical to the EpiPen): EpiPen Jr 150 mcg and EpiPen 300 mcg have been available since 2003; and Anapen Junior 150 mcg, Anapen 300 mcg and Anapen 500 mcg have been available since September 2021.
Adapted from ASCIA Guidelines.[6]

Adrenaline injectors

Adrenaline injectors (AIs) allow easy, reliable administration of adrenaline to treat anaphylaxis and are designed to be used by people without medical training. AIs can also be used in medical settings to reduce delays in administering adrenaline. Up to two adrenaline injectors may be prescribed on the PBS for a person considered to be at risk of anaphylaxis. Current prescribing guidelines require a patient to have been discharged from the emergency department or hospital after receiving adrenaline to treat anaphylaxis, or consultation with a clinical immunologist or allergy specialist, paediatrician or respiratory physician. Currently, there are two brands of adrenaline injectors available on the PBS, Anapen (150 mcg, 300 mcg and 500 mcg) and EpiPen (150 mcg and 300 mcg). A generic version from the same manufacturer as EpiPen is also PBS listed (Adrenaline Mylan 150 mcg and 300 mcg).

ASCIA has recently updated its recommendation for AIs for infants and young children in line with expert consensus.[3,8,9,21] ASCIA now recommends the AI 150 mcg for infants and young children weighing 7.5 to 20 kg, which was previously only recommended from 10 kg (Table 3). Although using a 150 mcg AI theoretically delivers up to 200% of the recommended adrenaline dose to an infant weighing 7.5 kg, use of the AI reduces delay and dosing errors compared with use of an ampoule and syringe when managing infants with anaphylaxis, and this is considered safe.[9,21,22] There is a theoretical risk of bone injury due to AI needles in infants less than 10 kg, but the risk may be reduced by only injecting into the thigh area, bunching the skin and muscle on the thigh before AI use and only holding the AI in place for the recommended time (three seconds for EpiPen, and 10 seconds for Anapen).[3,21,23]

In the absence of national referral pathways, we suggest that if the patient's primary care physician believes their patient requires an initial AI prescription, the doctor could contact either their local immunologist or the on-call service at their nearest teaching hospital for further advice.

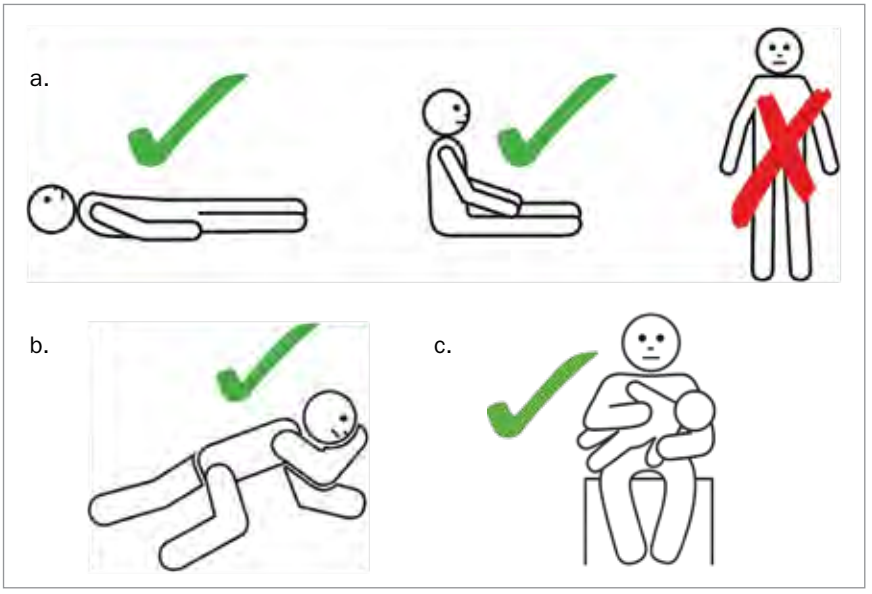

Figure. Correct positioning of patients with anaphylaxis. a (top). A patient experiencing anaphylaxis should lay flat or may sit upright with their legs extended if breathing is difficult. b (bottom left). Pregnant or unconscious patients should be placed in the recovery position. c (bottom right). Infants should be held horizontally or laid flat and not held upright.
Illustrations used with permission from the Australasian Society for Clinical Immunology and Allergy.

Practical tips for AI prescribing

Weight recommendations

ASCIA weight recommendations for use of AIs differ from the product information for all sizes of Anapen and EpiPen (Table 3). There are very limited data on efficacy and safety of adrenaline doses in anaphylaxis.[21] ASCIA's recommendations are based on current evidence and expert consensus. The ASCIA weight recommendations for AI reduce the risk of underdosing and have an excellent safety record.

Brand substitution

The Pharmaceutical Benefits Advisory Committee (PBAC) allows brand substitution by pharmacists for AIs for the 150 mcg and 300 mcg devices. Although the PBAC reiterates that different devices should not be prescribed for the same patient without training from the prescriber on a practical level, it is important to tick 'no brand substitution' or write the specific device you want to prescribe on electronic prescriptions to prevent substitution. The risk with substitution is patients being inadequately prepared to use their device and subsequent unnecessary delays in administration of adrenaline.

ASCIA action plans for anaphylaxis

ASCIA's action plans for anaphylaxis clearly outline the management of anaphylaxis and should be provided with an AI in all age groups. They are free to download and are available in Anapen, EpiPen and generic versions. The free AllergyPal app was developed by the Murdoch Children's Research Institute and allows patients to store an electronic copy of their signed action plan on their phone.

Supportive management

Allergen removal

Additional supportive management includes removal of the allergen, if present. For tick bites it is important to not forcibly remove ticks. The safest way to remove a tick is to kill it using an ether-containing solution and allow it to drop off ('freeze don't squeeze').[1,5] For patients with known tick anaphylaxis, the tick should only be removed under medical supervision.[5] For bee stings, flick out the sting as soon as possible using a fingernail or the edge of a credit card.

Positioning of the patient

Correct positioning of a patient with anaphylaxis is crucial and often overlooked. A patient may die if they sit or stand suddenly, as upright posture during anaphylaxis is associated with an increased risk of death.[1] A patient experiencing anaphylaxis should lay flat or may sit upright with their legs extended if breathing is difficult (Figure). Pregnant or unconscious patients should be placed in a left lateral (recovery) position and infants should be held horizontally and not upright over the shoulder.[6,9,10]

Patients should not be allowed to stand or sit for at least one hour after receiving adrenaline and four hours if they have received two or more doses, even if they appear to have recovered.[3,4,8] Patients should be transported to and from the ambulance on a stretcher or wheelchair even after adrenaline has been administered.

Oxygen administration

If available, high-flow oxygen should be given to all patients with anaphylaxis. Airway support should also be provided if needed.

Intravenous fluids

For hypotensive patients, give IV normal saline 20 mL/kg rapidly and consider additional wide-bore IV access. Tachycardia or floppiness may be signs of hypotension in infants.[6,10] Patients with cold-induced anaphylaxis should only receive warmed IV fluids.

Additional pharmacological treatments after IM adrenaline

Antihistamines and corticosteroids do not treat or prevent the cardiovascular or respiratory signs of anaphylaxis.[3,6,8] Nonsedating oral antihistamines may be given to help relieve urticaria and angioedema.

Injected promethazine should not be used in anaphylaxis because it can cause hypotension and muscle necrosis.

Corticosteroids have no place in the initial treatment of anaphylaxis, but they may be given after adrenaline in people with a history of reactive airways, or potentially to help prevent biphasic reactions (with minimal evidence).[5,8,12]

Salbutamol may be given for relief of bronchoconstriction in addition to adrenaline but should not be used in place of adrenaline. There is some evidence that high-dose inhaled salbutamol may help to relieve severe abdominal pain in food allergic reactions.[24]

Nebulised adrenaline (one nebule 1:1000) may be given to relieve upper airway obstruction in addition to IM adrenaline.

Duration of monitoring

ASCIA recommends that after administration of adrenaline a patient should be transported by ambulance to hospital for a minimum of four hours.[3,6] In remote areas where access to a hospital may not be feasible, a patient should be transported to a medical facility equipped for resuscitation.

ASCIA also recommends patients should be considered for overnight admission if they meet the following criteria:

- severe or protracted anaphylaxis (e.g. required repeated adrenaline doses or IV fluid resuscitation)
- a history of severe or protracted anaphylaxis
- concomitant illness (e.g. severe asthma, history of arrhythmia, systemic mastocytosis)
- live alone or are remote from medical care
- present for medical care late in the evening.

Minimal requirements on discharge

All patients at risk of re-exposure to their allergen, or for whom the allergen has not been identified, should be discharged with an AI or an authority prescription that should be filled immediately. Instructions regarding the recognition of anaphylaxis and the correct technique for the adrenaline injector should be provided. Each patient should have an appropriate ASCIA action plan for anaphylaxis.[5] ASCIA action plans for anaphylaxis, drug allergy and management of allergic reactions are available online (www.allergy.org.au/hp/anaphylaxis/ascia-action-plan-for-anaphylaxis/).

Minimum and evidence-based standards for the management of anaphylaxis are needed nationally across all healthcare sectors

Arrangements should be made for a consultation with a specialist allergist/immunologist and the patient should see their primary healthcare provider within a week of discharge. Patients with anaphylaxis usually see their primary healthcare provider annually for renewal of their AI authority prescription in between reviews with their allergy specialist. This is an excellent opportunity to refresh AI technique, revise signs and symptoms of anaphylaxis and discuss any reactions that have occurred since their last review. It is also important to optimise management of other conditions, such as asthma, to minimise the risk of fatal reactions.

Referral to a reputable national patient support organisation (see Box) is also recommended.

The need for a national minimum standard for the management of anaphylaxis

Minimum and evidence-based standards for the management of anaphylaxis are needed nationally across all healthcare sectors. Work is in progress towards implementing such standards in Australia with the hope of reducing fatalities, improving patient outcomes and providing clear guidance for healthcare professionals.

Conclusion

With increasing hospital admissions for anaphylaxis in Australia, it is likely that there is a parallel increase in patients with anaphylaxis presenting to primary practice with acute reactions as well as for follow-up care. Diagnosis is made on clinical grounds, and early recognition and appropriate prompt treatment reduce the risk of adverse outcomes. Adrenaline is the first-line treatment for anaphylaxis and should be given without delay by IM injection in the outer mid-thigh. There are no contraindications to giving adrenaline if anaphylaxis is suspected. ASCIA has recently updated its guidelines for the acute management of anaphylaxis in line with current evidence and provides online access to anaphylaxis resources to help health professionals provide both acute care and ongoing management for patients with anaphylaxis. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr Frith: None. Dr Joshi has participated on the Medical Advisory Board of Allergy and Anaphylaxis Australia.

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Updated anaphylaxis guidelines

A summary for primary care

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Managing mammalian meat allergy and tick anaphylaxis

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Tick-induced allergies, including mammalian meat allergy after tick bite and tick anaphylaxis, are increasingly prevalent, particularly on Australia's eastern seaboard. Tick bite prevention and appropriate management are crucial to both primary and secondary prevention of these allergies. Sensitisation to alpha-gal in mammalian meat can have many consequences, mostly affecting use of certain medical therapies.

KEY POINTS

- Tick-induced allergies are emerging worldwide, and tick anaphylaxis has caused fatalities in Australia.
- Mammalian meat allergy after tick bite (MMA) classically presents as severe anaphylaxis that is delayed (typically three to 6 hours after ingesting mammalian meat, i.e. 'middle of the night') and evolves rapidly in an individual with a past history of tick bite.
- The MMA spectrum comprises anaphylaxis, other systemic allergic reactions (urticaria and angioedema), gut-predominant symptoms, 'asymptomatic' alpha-gal sensitisation and, rarely, food-dependent carbohydrate-induced enterocolitis syndrome.
- Evidence-based tick bite prevention and management strategies are crucial to primary and secondary prevention of MMA and tick anaphylaxis.
- Consequences of developing alpha-gal specific IgE are myriad, affecting the use of medical therapies such as certain vaccines, heparin and cetuximab, and an increased burden of coronary artery disease.

In Australia, tick-induced allergies are the most common medical conditions caused by tick bites.[1] Tick-related allergies are the cause of many presentations to hospital emergency departments (EDs) in tick-hyperendemic regions. For example, a two-year survey of a NSW hospital ED found over 500 presentations of tick bite, 34 of which resulted in anaphylaxis.[2]

This article describes the spectrum of tick-induced allergies and their presentation, management and prevention.

Spectrum of tick-induced allergies

Tick-induced allergies comprise:

- mammalian meat allergy after tick bites (MMA), caused by allergy to the carbohydrate moiety alpha-gal in mammalian meat[3-5]
- rarely, probable T cell-mediated food carbohydrate-induced enterocolitis syndrome (FCIES)[6]
- large local reactions to tick bites and tick anaphylaxis, caused by allergies to tick salivary proteins.[1]

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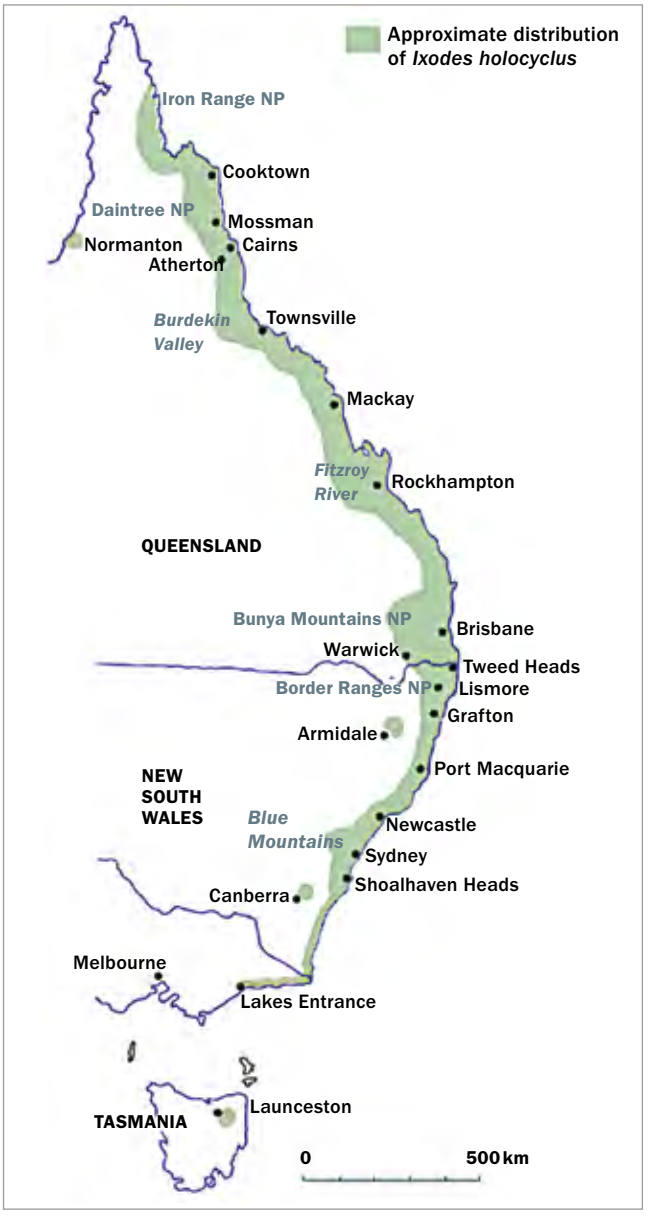


Figure 1. Distribution of the Australian paralysis tick (*Ixodes holocyclus*).
Adapted from Roberts FHS. Australian ticks. Melbourne: CSIRO; 1970, by TAGS Inc, Bill Conroy and Norbert Fischer.

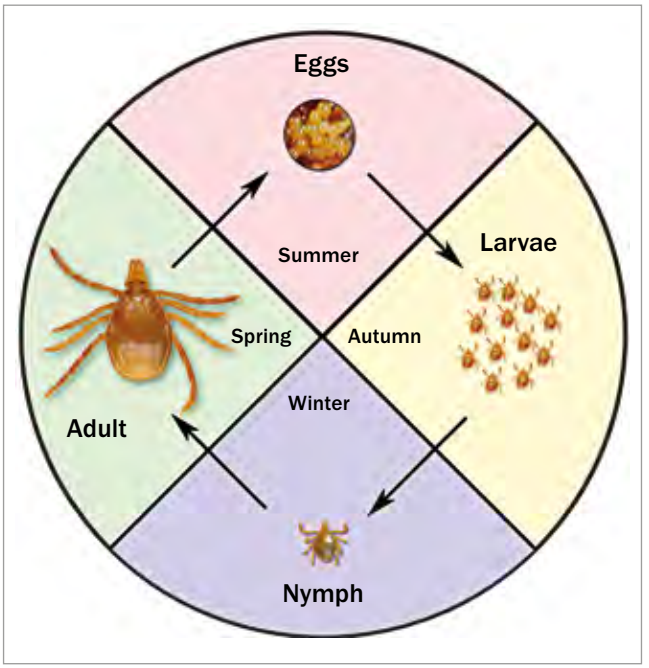


Figure 2. Life cycle of the Australia paralysis tick (*Ixodes holocyclus*).
Illustration courtesy of Stephen Doggett, Department of Medical Entomology, NSW Health Pathology, Institute for Clinical Pathology and Medical Research, Westmead Hospital, Sydney, NSW.

MMA is the most common tick-induced allergy. First described in 2007, MMA has now been reported in 18 countries worldwide, on every continent where humans are bitten by ticks.[1,3,4] Depending on the country, different tick species are involved in MMA.[1] In Australia, 95% of tick bites are caused by the Australian paralysis tick (*Ixodes holocyclus*), which is found along most of the eastern seaboard of Australia, from Lakes Entrance in Victoria to Cape York in Queensland (Figure 1).[1] A single bite of a nymph stage tick may trigger MMA, as can bites from adult ticks. The life cycle of *I. holocyclus* is shown in Figure 2. Because individuals who have been bitten only by larval ticks are rare, it is unclear whether larval tick bites alone can trigger the development of MMA.

Australia has the highest prevalence of MMA (113 per 100,000 population).[7] More than half of all Australians live in regions where *I. holocyclus* is endemic. The recent description in Western Australia of a second tick species able to cause MMA, *Ixodes* (*Endopalpiger*) *australiensis*, increases the number of people exposed in Australia to around 60%.[8]

In tick-endemic regions of Germany and the USA, sensitisation rates to alpha-gal allergen have been estimated to be as high as 35%, with MMA symptoms occurring in 8 to 9% of the population.[7] Most people with tick anaphylaxis also have specific IgE (sIgE) against alpha-gal but often have no clinical sensitivity to mammalian meat at the time of the tick anaphylaxis.[9]

Preventing tick-bite allergies

Evidence-based strategies for tick bite prevention and management have been developed with the aim of preventing tick-induced allergies. Research published in 2019 has verified the advice given since 2013 by the Australasian Society of Clinical Immunology and Allergy (ASCIA), Tick-induced Allergies Research and Awareness (TiARA) and the Emergency Care Institute New South Wales.[10]

1. PATIENT INFORMATION: TICK BITE PREVENTION AND MANAGEMENT

- Treat your backyard for ticks; consult a licensed pest controller
- Dress for the occasion
  - long-sleeved crew neck T shirt fitted at the wrists with a long tail to tuck into trousers
  - long trousers tucked into socks
- Use repellent (diethyltoluamide [DEET]) on areas unprotected by the above
- Obtain factory-bonded permethrin-treated clothing if you have tick-induced allergies or high-risk occupational or recreational pursuits (e.g. council workers, horticulturalists)
- Do not scratch anything you cannot see (because it could be a tick)
- Do not disturb a tick (because it will squirt allergen into you)
- Kill the tick in place
- For larval and nymph ticks, 'Dab it, don't grab it!'
  - use permethrin cream
  - scrape the tick off after 1 to 1.5 hours using a sharp-edged scraper
- For adult ticks (provided no previous anaphylaxis), 'Freeze it, don't squeeze it'
  - use a freezing agent
  - do not use 'bookmasks' that may be supplied with freezing agents as this may disturb the tick
  - ideally, wait for the tick to drop off or, if removed, this should be done by an expert using fine-tipped forceps
- Remember, 'Household tweezers are tick squeezers!'
- Watch the videos 'How to prevent tick bites' and 'How to remove a tick safely' (www.tiara.org.au)

The essential elements of recommended management of tick bites are:[10]

- kill the tick in situ by freezing
- after the tick is killed, allow it to drop off or, if removal is undertaken, this should be done by an expert using fine-tipped forceps
- avoid any compression of the tick, which will likely transmit tick saliva containing multiple salivary protein allergens as well as alpha-gal
- use tick repellent to help prevent tick bites; diethyltoluamide (DEET) is established as the most practical and effective tick repellent.[11]

Patient information on tick bite prevention and management is summarised in Box 1.

Allergies to tick salivary proteins

Large local reactions to tick bites

Large local reactions to tick bites are the least severe form of tick-induced allergy. The clinical features of large local reactions are summarised in Box 2.

Recommended management of a large local reaction to a tick bite comprises:

- elevation of the bite area above the level of the heart
- application of ice
- early use of oral antihistamines (which should be continued for seven to 10 days depending on duration of pruritus), and
- early use of a short course of moderate-dose corticosteroids (e.g. 50 mg for an adult daily for three days) or a single dose of dexamethasone 4 mg.

Often, large local reactions to tick bite are indistinguishable from cellulitis, and patients may be treated with antibiotics, sometimes parenterally, especially when the reaction affects the periorbital area. Patients who have experienced a large local reaction 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.

Tick anaphylaxis

Tick anaphylaxis is the most severe form of tick-induced allergy and was responsible for four deaths in Australia between 1997 and 2013.[12,13] Tick anaphylaxis, like MMA, is increasing in prevalence on the eastern seaboard of Australia. However, unlike MMA, tick anaphylaxis has rarely been recorded overseas, although reports of tick anaphylaxis are increasing from Spain and Japan.[14-17]

2. CLINICAL FEATURES OF LARGE LOCAL REACTIONS TO TICK BITE

- Large area of induration (more than 5 cm by 5 cm) at the site of a tick bite
- Occur with a bite of any life stage tick (usually nymphs or adults)
- Commence within 4 to 12 hours of the bite
- Attain maximum size by 48 to 72 hours after the bite
- Can be extensive, involving at least the joint above or below the bite
- Often are incapacitating
- Resolve completely within 7 to 10 days
- As the reactions resolve, the swelling moves downwards due to gravity
- Respond well to antihistamines and oral corticosteroids given early

Tick anaphylaxis is due to an IgE-mediated allergic reaction to one of five tick salivary proteins injected into the host by the tick when feeding.[18-22] Bites from nymph and larval ticks may prime the production of sIgE to tick salivary proteins; however, only the bite from an adult tick can trigger an episode of anaphylaxis, which occurs when the tick is disturbed by inappropriate handling.[23] Prevention of tick anaphylaxis involves preventing tick bites and managing any tick bite with evidence-based techniques (Box 3).

Mammalian meat allergy after tick bite

Alpha-gal is a carbohydrate formed from the combination of two galactose molecules by the enzyme alpha-galactosyltransferase. Alpha-gal is a constituent of the connective tissue of many mammals, but is not found in the tissues of humans, great apes or Old World monkeys. It is known to be present in tick saliva.[24] As alpha-gal is foreign to the human immune system, it stimulates the formation of IgG antibodies. Alpha-gal is also manufactured by the mucosal biome and coats the proteins of infectious agents on mucosal surfaces. This enhances the

3. SELF-MANAGEMENT OF TICK ANAPHYLAXIS

Any individual who has had tick anaphylaxis previously should:

- Be supplied with, and instructed in the use of, an epinephrine autoinjector
- Manage any further tick bite as follows:
  - leave the tick undisturbed
  - locate their epinephrine autoinjector
  - telephone 000 for transport to the nearest emergency department
  - not attempt to kill the tick or remove it at home
  - have the tick killed in situ in the emergency department and leave it to drop off
  - if the tick is removed, this should be done by an expert in the emergency department using fine-tipped forceps
  - avoid the use of plastic tweezers at the scene by ambulance officers (inappropriate as they may compress the tick)
  - use their epinephrine autoinjector as instructed if indicated

immune system's ability to recognise the pathogen and to mount an efficient IgG-based immune response.[25]

Although the immune response to alpha-gal is usually an IgG response, some predisposed individuals also elaborate IgE directed against alpha-gal.[20] When humans with sIgE against alpha-gal later ingest alpha-gal in mammalian meat or other products, they may develop an allergic reaction.

Features of MMA are shown in Box 4.[10,26,27] MMA does not occur in the absence of a tick bite, but some individuals may be unaware of having been bitten by a tick.[28] This may happen if they are visitors rather than residents in tick-hyperendemic area (e.g. the Northern Beaches area of Sydney, Maleny in Queensland, Denmark in Western Australia and Lakes Entrance, Victoria), especially if it is a nymph stage tick (2 mm long, resembling a black splinter) or is removed without being visualised (e.g. scratched from the scalp).

The MMA spectrum comprises:

- the classic presentation of mammalian meat anaphylaxis
- other systemic reactions (urticaria and angioedema)
- gut-predominant symptoms
- 'asymptomatic' alpha-gal sensitisation
- FCIES (uncommon).

An algorithm for the diagnosis and management of MMA is shown in the Flowchart.

Mammalian meat anaphylaxis

Presentation

The classic presentation of MMA is delayed anaphylaxis after a mammalian meat meal in an individual with a past history of tick bite. The reaction typically occurs three to six hours after ingesting mammalian meat (i.e. 'middle of the night'). The anaphylaxis evolves rapidly, is often severe and is due to intravascular basophil activation.[29] It occurs in people with a past history of tick bite, but as mentioned above this history may be difficult to elicit.[28]

Symptoms of mammalian meat anaphylaxis are those of anaphylaxis in general, except for the delay in onset. This delay is due to the time taken for the glycolipid allergen to be absorbed from the gut into intestinal lymphatics and thence the inferior vena cava, and to activate basophils in the circulation, thus triggering anaphylaxis.

Mammalian meat anaphylaxis may also present as anaphylaxis to gelatine. This is more likely after parenteral administration, for example in a vaccine such as Zostavax.

4. FEATURES OF MAMMALIAN MEAT ALLERGY

- Mammalian meat allergy (MMA) does not occur in the absence of a tick bite
- Not everyone bitten by a tick develops MMA
- Not uncommonly, more than one member of a family may develop MMA
- In people with MMA after a tick bite who have a subsequent tick bite, the level of alpha-gal-specific IgE (sIgE) can more than double[10]
- In people with MMA after a tick bite who avoid subsequent tick bites, the level of alpha-gal sIgE can reduce significantly within 18 months to two years[26]
- Some individuals with MMA after a tick bite who have no further tick bites and have a significant reduction in their alpha-gal sIgE levels may tolerate mammalian meats again after three to four years[27]
- Individuals who lose their tick-induced MMA and have a further tick bite can develop MMA again
- Blood groups A and O predispose to the development of alpha-gal sensitisation and thus MMA[26]

Diagnosis and management

Treatment of mammalian meat anaphylaxis is nonspecific and the same as for any patient with anaphylaxis. Provision of an epinephrine autoinjector, instruction in its use and an anaphylaxis action plan are essential.

Diagnosis of mammalian meat anaphylaxis depends on the clinical features. Radioallergosorbent (RAST) 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. Measurement of the convalescent tryptase level is prudent to exclude coincident mastocytosis.

Patients diagnosed with MMA require dietary advice from an accredited practising dietitian, with supplementary information available from TiARA (www.tiara.org.au). For patients who have had mammalian meat anaphylaxis, initial strict avoidance of mammalian meats is recommended.

Some people with mammalian meat anaphylaxis also react to mammalian meat vapours (e.g. barbecue meat fumes).[30]

A minority of individuals who have experienced mammalian meat anaphylaxis will also react to mammalian milk and milk products. Typically, they react to soft cheeses and cheeses containing animal rennet (in some imported cheeses) but tolerate hard cheeses. Mammalian milks and their products should be excluded only if they cause symptoms at any stage.

Patients who are negative for sIgE to bovine gelatine usually tolerate oral gelatine, but parenteral gelatine (e.g. in certain vaccines) should usually be avoided.[31]

Patient education is essential for people with MMA about:

- prevention and management of further tick bites (Box 1)
- the risks of alpha-gal sensitisation (see below).

Provided the patient has no 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.[32]

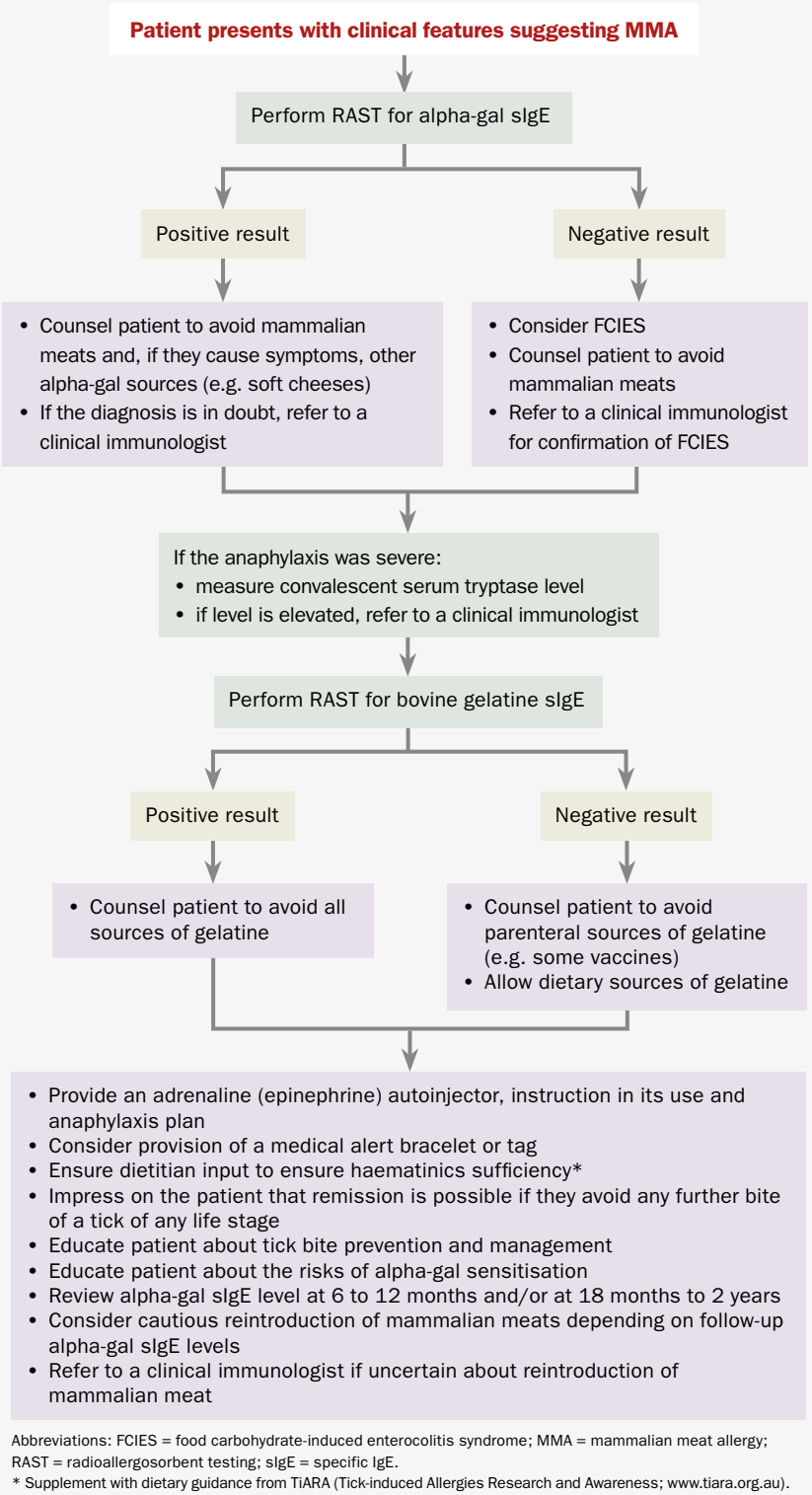
Other systemic reactions (urticaria and angioedema)

MMA can also manifest as typical urticaria and angioedema appearing three to six hours after mammalian meat ingestion. Lesions may occur at the site of a previous tick bite.

Treatment is as for urticaria and angioedema in general. Further management includes dietary advice and education about tick bite prevention and management and the risks of alpha-gal sensitisation, as for patients with mammalian meat anaphylaxis. However, for people with urticaria and angioedema, further symptoms can usually be prevented by:

- avoiding amplifying factors with mammalian meat ingestion (see below)
- eating small portions of mammalian meats
- avoiding products with higher concentrations of alpha-gal such as offal.

DIAGNOSIS AND MANAGEMENT OF MAMMALIAN MEAT ALLERGY



Abbreviations: FCIES = food carbohydrate-induced enterocolitis syndrome; MMA = mammalian meat allergy; RAST = radioallergosorbent testing; sIgE = specific IgE.
* Supplement with dietary guidance from TiARA (Tick-induced Allergies Research and Awareness; www.tiara.org.au).

5. POTENTIAL AMPLIFYING FACTORS IN MAMMALIAN MEAT ALLERGY[33-36]

- Greater amount of mammalian meat or meat product consumed
- Concomitant alcohol consumption
- Sleep deprivation
- Exercise (within two hours usually)
- Cooking (slow cooking and re-heating break down the connective tissue in meat, increasing alpha-gal availability)
- Offal consumption (e.g. sausage encasings, liver, kidney), as offal contains higher concentrations of the alpha-gal allergen
- Use of spices, especially chilli (but not nutmeg, black pepper or bay leaf)
- Prior NSAID within 24 hours
- Recent illness (e.g. upper respiratory tract infection)
- Perimenstrual phase

Cured meats (e.g. bacon, ham and prosciutto) are often tolerated in small amounts. As with mammalian meat anaphylaxis, mammalian milks and their products should be excluded only if they cause symptoms. Oral gelatine is usually tolerated by those who are negative for sIgE to bovine gelatine, but parenteral gelatine should usually be avoided, even in this group. Reintroduction of mammalian meats should again be guided by a reduction in alpha-gal sIgE levels.

Gut-predominant symptoms

Some people experience gut-predominant symptoms after mammalian meat ingestion. Colicky abdominal pain is a feature. Nausea may precede the pain, and diarrhoea is common. Urticarial lesions and patchy erythema may be present.

Antihistamines and corticosteroids are usually not helpful for gut-predominant symptoms. Epinephrine is not indicated and does not improve gut symptoms if used. The recommended dietary and other advice is similar to that for people with MMA manifesting as urticaria and angioedema.

Food-dependent carbohydrate-induced enterocolitis syndrome

FCIES affects 1% of people who react to mammalian meat.[6] Symptoms are the same as those of food-dependent protein-induced enterocolitis syndrome (FPIES), as follows.

- Protracted severe vomiting and diarrhoea are features
- Hypotension often occurs (due to a fluid phase shift to the gut)
- Pallor and lethargy are typical (in contrast to IgE-mediated reactions where erythema is usual).

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

Dietary advice for people who have experienced FCIES is similar to that for people with mammalian meat anaphylaxis. Reintroduction of mammalian meat may be possible in future years, provided there is no subsequent bite from a tick at any life stage. However, there is no in vitro test to guide mammalian meat reintroduction in people with FCIES and no current evidence specifically regarding the likely success and timing of this reintroduction.

Role of amplifying factors in MMA

Certain factors (cofactors) around the time of food ingestion can amplify reactions to food allergens in general and in MMA (Box 5).[33-36] For example, in people with peanut allergy, the dose of peanut required to elicit an allergic reaction is reduced by 45 to 61% when they have exercised within two hours of eating and by 45% when they are sleep deprived.[36] More than one amplifying factor may operate in a single episode of allergic reaction.

Consequences of alpha-gal sensitisation

'Asymptomatic' individuals with alpha-gal sensitisation (i.e. they have developed sIgE to alpha-gal but are not clinically reactive to mammalian meats) may constitute up to 25% of the population in tick-hyperendemic regions.[7] After two tick bites, up to 50% of individuals may be sensitised to alpha-gal.[17]

Almost all individuals with alpha-gal sIgE levels greater than 5.5 kU/L have symptomatic MMA after mammalian meat ingestion (more than 95% probability).[32] Among individuals with lower levels of alpha-gal sIgE (less than 5.5 kU/L), about two-thirds will have symptoms when they ingest mammalian meats or products in the presence of an amplifying factor.

Other potential consequences of developing alpha-gal sIgE are myriad, mostly affecting the use of medical therapies.

6. THERAPEUTIC AGENTS WITH POTENTIAL FOR ANAPHYLAXIS IN PATIENTS WITH ALPHA-GAL SENSITISATION AND MMA

- Cetuximab (a murine-derived cancer therapy)[37,38]
- Gelatine-containing vaccines (e.g. Zostavax)[39]
- Heparin (porcine derived)
- Cell savers containing gelatine, if the gelatine leaks into the tissues
- Gelatine capsules in highly allergic individuals
- Porcine heart valve prostheses (with potential for reduced valve lifespan)[40]
- Colloid solutions (rarely used)
- Mammalian-derived excipients in medications (e.g. magnesium stearate, which is of animal origin in about two-thirds of cases) – these can cause symptoms in a small minority of patients with MMA
- Antivenoms (e.g. snake bite antivenoms, although these should be administered nevertheless)

Abbreviation: MMA = mammalian meat allergy.

Therapeutic implications

Therapeutic agents with potential for causing anaphylaxis in people with alpha-gal sensitisation and MMA are listed in Box 6.[37-40] These include the murine-derived monoclonal antibody cetuximab, used to treat colon and head and neck

7. PATIENT AND HEALTH PRACTITIONER RESOURCES ON TICK ALLERGIES

ASCIA (Australasian Society of Clinical Immunology and Allergy)
- Tick allergy. Information for patients, consumers and carers (www.allergy.org.au/patients/insect-allergy-bites-and-stings/tick-allergy)
- Animation: How to remove a tick (www.allergy.org.au)

TiARA (Tick Induced Allergies Research and Awareness, www.tiara.org.au)
- Videos: 'How to prevent a tick bite' and 'How to remove a tick safely'
- Tick anaphylaxis and mammalian meat allergy resources
  - Pamphlet: Allergic conditions caused by ticks
  - Pamphlet: Preventing and managing tick bites
  - Powerpoint: Allergies provoked by ticks
- Mammalian meat and mammalian produc-free dietary resources
  - Mammalian meat allergy chef card
  - Dietary information
  - Guidelines on diet, dietary iron

Allergy and Anaphylaxis Australia (www.allergyfacts.org.au)

Department of Medical Entomology, The University of Sydney and Westmead Hospital (www.medent.usyd.edu.au)

Australasian Mastocytosis Society (www.mastocytosis.org.au)

Reviews for health professionals
- van Nunen SA. Tick-induced allergies: mammalian meat allergy and tick anaphylaxis. Med J Aust 2018; 208: 316-321.
- van Nunen S. Tick-induced allergies: mammalian meat allergy, tick anaphylaxis and their significance, Asia Pac Allergy 2015; 5: 3-16.

cancers. There is a 6.9% risk of anaphylaxis with cetuximab use in Northern Sydney, with 59 cases, including two fatalities, reported to the TGA Database of Adverse Event Notifications up to July 2020 (www.tga.gov.au/database-adverse-event-notifications-daen).[37,38] Current best practice is to check for alpha-gal sIgE before use of cetuximab. Low levels of alpha-gal sIgE may be associated with life-threatening anaphylaxis, even where mammalian meats are tolerated, typically with the first cetuximab dose.[37,38]

Gelatine-containing vaccines such as Zostavax can cause anaphylaxis, with one formal and several anecdotal reports.[39] Mammalian-derived excipients in medications can cause symptoms in a small minority of patients with MMA. For example, magnesium stearate in medications is of animal origin in about two-thirds of cases. This is often undeclared, and patients need to check with the pharmaceutical company supplying the drug in Australia.

Alpha-gal sensitisation and atherosclerosis

In people younger than 65 years, alpha-gal sensitisation has been associated with more extensive coronary artery atherosclerotic plaque and more unstable atherosclerotic plaque.[41] Preliminary findings of a study in a large Australian cohort support this risk.[42] Tick bites constitute a major public health problem on this basis alone.

Reintroduction of mammalian meats

Almost invariably, levels of alpha-gal sIgE in people with MMA are higher against bovine thyroglobulin alpha-gal than against beef, followed by pork, and lowest against lamb and mutton. However, reintroduction of mammalian meat usually begins with cured pork products such as bacon and prosciutto and then ham (providing these foods are allowed in the patient's usual diet) as these are the mammalian meats most likely to be tolerated.

The patient should begin with a piece of meat the size of a grain of rice, eaten early in the day to avoid the three to six hour delay obscuring milder symptoms during sleep. If this is tolerated, they can progressively double the amount of meat consumed on any day it is convenient until a portion size is reached. If cured pork meats are tolerated then lamb (e.g. lamb cutlet) can be introduced in the same manner, followed by fresh pork and thereafter fresh beef.

Spices and chilli should be avoided, as should raw, reheated or slow-cooked meat, at least until tolerance for the particular mammalian meat is confirmed. The patient should be advised to avoid amplifying factors initially on the days meat is being eaten.

Conclusion

Tick-induced allergies (MMA and tick anaphylaxis) are increasing in prevalence, particularly on Australia's eastern seaboard. Resources on tick allergies for patients and medical practitioners are listed in Box 7. Tick bite prevention and management are crucial to both primary and secondary prevention of tick-induced allergy. Sensitisation to the allergen alpha-gal in mammalian meat has myriad potential consequences, mostly affecting use of particular therapies. Confirmation of the association between alpha-gal sIgE and atherosclerosis severity, however, means that tick bite prevention and management campaigns will be even more important in keeping Australians safe from the sequelae of tick bites. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Assessing and managing IgE-mediated food allergies in children

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The incidence of food allergy, and particularly peanut allergy, has increased substantially in Australia over the past decade. A thorough clinical history and specific testing should be conducted to identify the allergen. Allergen avoidance and education are currently the mainstays of treatment.

KEY POINTS

- More than one-third of children with IgE-mediated food allergy will react on their first known ingestion of a food.
- Cow's milk, egg, peanut, tree nuts, fish, shellfish, soy and wheat cause more than 90% of food allergies in children.
- Exclusion diets should only be undertaken with specialist advice because they may inadvertently worsen, rather than aid, the child's situation.
- Foods already tolerated in the child's diet should not be removed if a skin prick test or serum-specific immunoglobulin E to that food is positive but there are no clinical signs of allergy to that food.
- New evidence suggests that early introduction and regular ingestion of certain allergenic foods significantly reduces the risk of developing food allergy.
- There is currently no scientific evidence to suggest anaphylaxis can occur from skin contact with an allergen.

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Food allergy is an increasingly common problem that affects about one in 10 babies (up to 12 months old) in Australia.[1] Furthermore, the incidence of peanut allergy has undergone a 100% increase over the past 10 years.[2,3]

The mainstays of treatment of children with immunoglobulin E (IgE)-mediated food allergy are correct allergen identification and avoidance, education about management of an acute reaction and optimal treatment of other atopic conditions, particularly asthma. Future treatments may include oral desensitisation. This article discusses IgE-mediated food allergy in children and strategies for its management.

Defining food allergy

A food allergy is an adverse reaction to a generally harmless substance within a food (usually a protein) that is mediated by the immune system. There are essentially three main types of food allergy: IgE-mediated, nonIgE-mediated, and mixed IgE- and nonIgE-mediated. Food may also cause symptoms through nonimmune mechanisms such as lactase deficiency, but this is not defined as a food allergy.

Why is food allergy increasing?

The two main factors that influence the development of allergies are:

- genetics
- the environment.

It seems unlikely that the genetic make-up of humans would have changed significantly in the past 10 to 15 years, so genetic changes do not account for the increase in childhood allergy over this time.

Although there are several theories that have been studied in relation to the increase in food allergy, the hygiene hypothesis

is one of the most commonly cited. However, it seems unlikely that a single factor would account for the complexities of these diseases.

Recent studies have suggested a role of exposure to endotoxins from farm animals in both pregnancy and early childhood as a protective factor against developing allergies.[4] It may be that the early response of the immune system to these endotoxins decreases the likelihood of developing an atopic response. Changes to our diet and food processing methods may potentially be a factor in the rise in food allergy. Thermal food processing techniques may inadvertently increase the allergenicity of certain foods; for example, roasted peanuts are more allergenic than raw or boiled peanuts. Also, the type and diversity of the gut microbiota and the timing of exposure to an allergen, as well as the route of initial exposure (e.g. gut versus epicutaneous), are under intense study.

Foods implicated in food allergies

- More than 90% of food allergies in children are caused by cow's milk, egg, peanut, tree nuts, fish, shellfish, soy and wheat.[5]
- It is important to note that any food is potentially allergenic. In adults, most food-related anaphylaxis is caused by peanut, tree nuts or seafood.[6]
- Cow's milk and egg are also implicated as leading causes of anaphylaxis in young children.[7,8]

IgE-mediated food allergy

IgE-mediated food allergy refers to immediate-type hypersensitivity reactions that occur because specific IgE against that particular allergen is produced. Theoretically, on first exposure to the allergen, the body recognises this protein as foreign and plasma cells produce IgE directed against the allergenic component of that protein. The IgE then sits on the surface of mast cells that are located in various tissues of the body including the skin, the lining of the lungs and mucosa.

On next exposure, the allergen cross-links the specific IgE molecules, resulting in the mast cells releasing granules containing several inflammatory mediators including histamine. These mediators act on the end organs, including blood vessels, bronchioles and mucosal tissues, resulting in the symptoms and signs of an acute allergic reaction. More than one-third of children with IgE-mediated food allergy will react on their first known ingestion of a food, and sensitisation may have occurred via the skin, particularly in infants with a break down in skin barrier function such as with eczema.[9-11]

Oral allergy syndrome or pollen-food syndrome (IgE-mediated)

Some patients with seasonal allergic rhinitis/conjunctivitis experience itch and irritation of the tongue, mouth and throat after ingestion of some fresh fruits and vegetables. Most of these patients are allergic to cross-reactive proteins common to some pollen and foods, and the condition is known as oral allergy syndrome or pollen-food syndrome. Treatment of patients with this condition involves either avoiding the food or eating it in the cooked form only (if tolerated).

1. SYMPTOMS AND SIGNS OF IgE-MEDIATED FOOD ALLERGY IN CHILDREN

Mild-to-moderate allergic reaction

- Urticaria
- Lip/mouth swelling (angioedema)
- Vomiting/diarrhoea/abdominal pain
- Acute rhinitis

Severe allergic reaction or anaphylaxis

- Difficulty breathing/noisy breathing
- Swelling of the tongue
- Swelling or tightness in the throat
- Difficulty talking and/or a hoarse voice
- Wheeze or persistent cough
- Loss of consciousness and/or collapse
- Young children may become pale and floppy

Diagnosing IgE-mediated food allergy

Most cases of IgE-mediated food allergy are fairly easy to recognise. Symptoms generally appear within 30 minutes of ingesting the allergenic food (although they may start up to two hours later) and can occur on the first known exposure to that food. Most food allergic reactions are relatively mild. The symptoms and signs of a mild-to-moderate allergic reaction may include one or more of the following: urticaria, lip and/or mouth swelling (angioedema), vomiting, diarrhoea, abdominal pain and/or acute rhinitis.

Signs of a severe allergic reaction or anaphylaxis may include one or more of the following: difficulty breathing, noisy breathing, swelling of the tongue, swelling and/or tightness in the throat, difficulty talking, a hoarse voice, wheeze, a persistent cough (sometimes described as staccato), loss of consciousness and/or collapse (Box 1). Affected young children may become pale and floppy (a sign of hypotension). More than 90% of children

2. DIAGNOSING FOOD ALLERGY IN CHILDREN: TIPS FOR GPS

- Taking a detailed patient history at the time of presentation is extremely helpful: patient recall about foods, including brands and timing of ingestion, is usually much better at the time of a reaction
- Recognise that not all food reactions are IgE-mediated allergies
- Counsel parents about the primary importance of treating the child's skin topically in cases of atopic dermatitis rather than manipulating diets without evidence, which may increase the risk of allergy
- Counselling parents about the relevance of allergy tests to their child's condition can help to prevent unnecessary anxiety, investigations and food restrictions
- If ordering in-vitro-specific IgE tests, specify which allergen you wish to test; avoid ordering 'food panels'

will have cutaneous symptoms before they develop more severe symptoms; however, the reaction can evolve very rapidly. The diagnosis may be less obvious when the trigger food is not easy to identify on history or the symptoms are less defined (Box 2).

As food allergy is rarely a trigger for chronic rhinorrhoea, in general, foods should not be removed from the diet in order to treat rhinitis.

It is also important to note that babies have delicate skin and as such, perioral erythema is most likely to be due to contact irritation. Foods such as concentrated tomato and citrus fruits may irritate the skin, especially when the infant self-feeds. This is not a food allergy.

Atopic dermatitis and food allergy

Food allergy does not cause atopic dermatitis but may be co-associated. Evidence would suggest that only up to 50% of children with moderate-to-severe atopic dermatitis have a true food allergy.[12,13] Delayed reactions to foods can occur in patients with atopic dermatitis and are not primarily IgE-mediated.

A short period of elimination of potentially allergenic foods may be trialled by specialists in conjunction with dietitians in a minority of patients. However, these diets are difficult and may not yield results. Severe allergic reactions have been reported on re-exposure of children to foods removed from their diet for prolonged periods of time. Therefore, exclusion diets should only be undertaken with specialist advice because they may inadvertently worsen, rather than aid, the child's situation.

In managing children with atopic dermatitis, treating the underlying skin disorder with emollients and appropriate topical corticosteroids is the most important intervention, not removal of foods.

Investigating food allergy

There are several tests available for identifying the likely cause of a food allergy.

Skin prick tests

Skin prick tests have the advantage of being more sensitive than blood tests for allergen-specific IgE and are the first-line investigation for most immunologists/allergists in Australia. They provide immediate results, are usually well tolerated and rarely cause severe side effects. If an allergy to a fruit, vegetable or processed food is suspected, it is helpful for the patient to bring a sample of that food to the specialist appointment for fresh food testing. Antihistamines should be stopped for three to five days before testing.

Skin prick tests can be performed in patients of any age but require careful interpretation in young infants. The risk of a more severe reaction to a skin test is higher in a young baby (under 12 months).[14] Skin prick testing has no role in confirming suspected reactions to food additives or food intolerances.

Blood tests for allergen-specific IgE

Enzyme and fluorescent-based assays called 'in vitro-specific IgE testing' or 'serum-specific IgE testing' (ssIgE) has replaced the radioallergosorbent test (RAST). If skin prick testing is not available, there is no clear skin on which to perform the test or the patient cannot stop taking their antihistamines, an ssIgE test may be useful. Testing of specific antigens should be ordered rather than 'food panels'. Results of food panels are confusing and parents often think that all the foods in the panel are to be eliminated from the diet if a result is positive. This can lead to unnecessary and potentially dangerous restrictions.

Allergen component-resolved diagnostic testing (CRD) is relatively new. It uses purified or recombinant allergens (rather than a crude extract of the food) to identify the specific molecules causing sensitisation.[15] The value of these tests in Australia still needs to be carefully studied and, therefore, they are not recommended by the authors for routine allergy testing by GPs. They may be used in the specialist setting in some cases.

It is important to note that the magnitude of a skin test reaction or ssIgE result correlates with the likelihood of the patient having a clinical allergy to that food, not with the severity of the reaction. A positive skin test or ssIgE signifies allergic sensitisation and not necessarily clinical allergy.

Tests for IgE-mediated food allergy should be ordered and interpreted alongside a detailed clinical history. In general, foods already tolerated in the diet should not be removed, even if a skin prick test or ssIgE to that food is positive.

Total IgE levels

The total IgE value is often raised in people with allergies and or eczema. However, measurement of the total IgE level does not help in the diagnosis of a food allergy.

Oral food challenges

The gradual feeding of a test food under close supervision, with observation as to

3. PREVENTING FOOD ALLERGY IN CHILDREN[15]

The Australasian Society of Clinical Immunology and Allergy (ASCIA) guidelines for infant feeding and allergy prevention are summarised below.

- Breastfeeding is recommended for at least six months
- Breastfeeding during the period of weaning to solid foods may help to reduce the risk of allergies but the evidence for this is low
- If the child is not breastfed or is receiving supplemental formula feeds, a standard cow's milk formula can be given. There is no convincing evidence to suggest that partially or extensively hydrolysed formulas help prevent food allergy, eczema, asthma or allergic rhinitis in infants or children. Similarly, there is no evidence to support the use of soy or other mammalian milk formula in preference over cow's milk formula in allergy prevention
- Solid foods can be introduced at about 6 months of age but not before 4 months
- If a food is tolerated, continue to regularly include this in the infant's diet
- Avoidance of potentially allergenic foods is not recommended. Previous guidelines suggested avoiding allergenic foods such as cow's milk and egg until 12 months of age but new evidence supports early introduction of allergenic foods

Other advice

- Smoking during pregnancy or in the presence of children is to be avoided
- Diets should not be restricted during pregnancy. Not only is this unhelpful in preventing allergic disease but it may also cause nutritional difficulties in the mother and the child

whether it is tolerated, is sometimes performed to prove a diagnosis of food allergy when the history is not entirely clear. An oral food challenge may also be used to determine if a food allergy has resolved. Oral food challenges must always be performed by experienced clinicians who have the ability to recognise and manage a patient with anaphylaxis. Extensive resuscitation equipment should be readily available.

Unproven methods

Examples of unproven methods of assessing food allergy include cytotoxic food testing, kinesiology, Vega testing, electrodermal testing, pulse testing, reflexology and hair analysis. These tests have not been scientifically validated and may lead to dangerous avoidance strategies.[16]

The natural history of food allergy

Most common childhood food allergies resolve before adulthood, although the timing can be variable and difficult to predict. There appears to be a trend to outgrowing allergies at a slower rate.[17] Although many children still attain tolerance at a young age, some will take until adolescence to outgrow their allergy, with about 70% achieving tolerance to egg and milk allergens by 16 years of age.[17,18] Unfortunately, only about 20% of children will outgrow peanut, tree nut or seafood allergies,[19-21] and a number of these may lose their tolerance to the allergen if continued regular exposure to the allergen does not occur.

Allergy prevention

Prevention of allergic disease including food allergy remains an active and evolving area of research. New evidence suggests that early introduction and continued ingestion of allergenic foods significantly reduces the risk of developing food allergy.[22,23] The Learning Early about Peanut (LEAP) study demonstrated that in high-risk infants (those with severe eczema and/or an IgE-mediated egg allergy), introduction of peanut before the age of 1 year and regular ingestion reduced the incidence of peanut allergy by 80%.[23]

Based on new evidence, the Australasian Society of Clinical Immunology and Allergy (ASCIA) has recently published revised infant feeding guidelines that suggest an approach to preventing food allergy (Box 3).[24] Although the guidelines (summarised below) still recommend the introduction of solid foods at about 6 months of age, but not before 4 months, they have changed to actively encourage the introduction of allergenic foods in the first year of life.

4. USEFUL RESOURCES

- **Australasian Society of Clinical Immunology and Allergy (ASCIA)**
  http://www.allergy.org.au.
  The ASCIA website provides up-to-date evidence-based resources for doctors and their patients, including anaphylaxis action plans and advice on infant feeding and food allergies (general and to specific foods). The site also has an e-learning package for parents to provide education about the management of children with anaphylaxis
  - information on food allergy including diet sheets listed at: www.allergy.org.au/patients/food-allergy
  - information on allergy prevention listed at: https://www.allergy.org.au/patients/allergy-prevention
  - information on anaphylaxis, including action plans and information on adrenaline autoinjectors listed at: www.allergy.org.au/health-professionals/anaphylaxis-resources
- **Sydney Children's Hospital Network**
  http://schn.health.nsw.gov.au
  The Sydney Children's Hospital Network website provides fact sheets for parents on allergen avoidance and other useful advice about food allergy
- **Anaphylaxis nurse educators**
  Nurse educators are available to visit schools in New South Wales, Western Australia and parts of Queensland to educate teachers about the management of anaphylaxis. Anaphylaxis nurse educators are based at The Children's Hospital at Westmead, Sydney

5. MANAGING CHILDREN WITH FOOD ALLERGY: TIPS FOR GPS

- Identify the potential allergen or allergens
- Provide the tools and knowledge to avoid the allergen (see useful resources in Box 4)
- Ensure adequate nutrition
- Prescribe emergency medications if appropriate and educate the family how to recognise and manage an allergic reaction (see useful resources in Box 4)
- Optimise treatment for the concurrent atopic diseases

Management of food allergies

Currently, there is no cure for food allergy and management of affected patients involves avoiding the food allergens. However, accidental ingestions of the allergenic food are not uncommon. Providing clear written information to patients and their families about how to avoid allergens is helpful because food labelling can be confusing. In addition, written action plans to guide the management of children with acute reactions should be provided to patients (dietary information sheets and action plans are available from ASCIA; Box 4).

Potential pitfalls of food avoidance are nutritional inadequacy and psychological difficulties. If a major staple food such as cow's milk is removed from a child's diet, advice from a dietitian is important in order to assess adequate nutritional intake. Children with gross calcium deficiencies and even malnutrition are seen in specialist clinics after being placed on restricted diets.

Box 5 provides some tips for GPs managing children with food allergies.

Future treatments

Numerous trials are under way around the world seeking a better solution for the management of people with food allergies. These include oral, sublingual, subcutaneous and epicutaneous food immunotherapies, with or without adjuvants.[25] Although results are promising, these therapies are not yet ready for clinical use. Many of the patients using these therapies achieve desensitisation, particularly with ongoing consumption of the allergen, but far fewer develop sustained oral tolerance. Optimising oral tolerance while maintaining an acceptable safety profile are the two main barriers to food immunotherapy at present.

Several studies have shown that even in infants with anaphylaxis to cow's milk or egg, about 70% can tolerate milk or egg in a baked product such as a muffin or cake.[1,26-28] This is because the protein is altered by heat and probably because the food matrix has a modifying effect on the allergen absorption. Challenging the allergic child to these allergens should be closely supervised by a specialist. If the baked proteins are tolerated, regular consumption may lead to faster resolution of the allergy. If the child is already tolerating baked egg or milk but has an allergy to the unmodified protein, the baked product should not be removed from their diet.

When to refer

Tips for which patients with food allergies to refer to a specialist are listed in Box 6.

6. REFERRAL OF CHILDREN WITH FOOD ALLERGY

Children with food allergy should be referred to a specialist in the following circumstances:

- all cases of suspected anaphylaxis
- any child at high risk of anaphylaxis, e.g. children with asthma as well as food allergy
- milder cases of suspected food allergy where the cause cannot be identified with certainty
- cases of suspected nonIgE-mediated allergy such as food protein-induced enterocolitis syndrome or eosinophilic oesophagitis
- very young children (under 2 years of age) in whom tests are likely to be more difficult to interpret and weaning and nutritional issues are especially important
- if more than one staple food is to be eliminated (advice from dietitian also required)

Anaphylaxis

Fatalities from anaphylaxis are extremely rare. There is currently no scientific evidence to suggest anaphylaxis can occur from skin contact with an allergen.

Risk factors for anaphylaxis

There is no test that can rule out anaphylaxis for a child with food allergy. There are, however, several epidemiological factors that have been found to be associated with anaphylaxis fatalities and/or may favour the provision of the child with an adrenaline autoinjector. There is also increasing evidence that concurrent presence of other atopic diseases is associated with increased severity of signs during a food allergic reaction. These factors include:

- a history of previous anaphylaxis
- asthma
- association with a particular allergen (i.e. peanut or tree nut, especially cashew)
- having a previous significant reaction to a very small amount of that protein
- the child's age; for example, the risk of fatality is higher in adolescence and young adulthood than at other ages
- lack of access to emergency medical care.

Management of anaphylaxis

Although it is beyond the scope of this article to discuss anaphylaxis management in detail, the first line of management in the acute setting is intramuscular adrenaline 1:1000 at a dose of 0.01 mL/kg to a maximum of 0.5 mL into the lateral thigh. This should be repeated after

five minutes if the patient is not improving.

Antihistamines may reduce the skin and gastrointestinal symptoms of an allergic reaction but do not treat or prevent anaphylaxis. Oral corticosteroids are not the first-line treatment for a patient with anaphylaxis.

If a child is considered at risk of anaphylaxis then an adrenaline injector device should be prescribed. Two devices are now available in Australia on the PBS: Anapen (150 mcg, 300 mcg and 500 mcg) and Epipen (50 mcg and 300 mcg), although other brands are available in other countries. ASCIA recommends that the 150 mcg junior devices are prescribed for infants and children weighing between 7.5 and 20 kg and a 300 mcg device for individuals weighing more than 20 kg. Anapen also has a 500 mcg device. For individuals wighing over 50 kg, either a 300 mcg or 500 mcg device can be prescribed.[29] Note that these recommendations differ from the product information for the autoinjectors, which states that the 0.15 mg adrenaline dose versions are intended for children weighing between 15 and 30 kg, and the 0.30 mg adrenaline dose devices for children and adults weighing more than 30 kg. The ASCIA recommendations are closer to the recommended dose of adrenaline that would be given for anaphylaxis if a patient was treated in hospital (e.g. 0.01 mL/kg adrenaline 1:1000, maximum of 0.5 mL).

Conclusion

The rate of food allergy is increasing, as is the rate of anaphylaxis to food. Thankfully most food allergy is mild and fatalities are rare. GPs play a vital role in managing affected patients because they are usually the first to see the child after an allergic reaction. It is important to take a detailed history and to provide this to the specialist if referral is appropriate. Treating co-existing atopic conditions is helpful in the overall management of a child with food allergy. Reassuring parents, providing evidence-based resources and discouraging unsupervised dietary restriction will help optimise the child's nutritional status. Recognising anaphylaxis and the risk factors can be life-saving. Prescribing adrenaline autoinjectors appropriately and educating parents in using the device is a service that GPs can provide in conjunction with a specialist. MT

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References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Assessing and managing IgE-mediated food allergies in children

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PEER REVIEWED FEATURE

Beware of allergic reactions to stings and bites

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Stings and bites from insects and ticks commonly cause allergic reactions, ranging from a local swelling to major anaphylaxis. Each patient responds in a unique way and the best course of action must be determined, taking several factors into account, including identification of the offending insect and the severity of the reaction.

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KEY POINTS

- Life-threatening allergic reactions to stings or bites from insects and ticks are relatively common.
- The insects responsible include honey bees; paper, mud and European wasps; and ants.
- Allergic reactions to bites and stings develop rapidly, peak quickly and usually ease within a day or two.
- Adverse reactions range from large local swellings arising from the sting or bite site to systemic responses confined to the skin and anaphylaxis.
- The most effective method to reverse anaphylaxis is an injection of adrenaline. Killing embedded ticks in situ reduces the risk of allergic reaction.

Australia has a wide diversity of stinging and biting insects and arachnids capable of causing severe life-threatening allergic reactions. Measures are available to prevent these events and treat patients when reactions do occur. This article deals with terrestrial but not marine creatures, nor does it deal with the occasional anaphylaxis to snake venom in heavily exposed snake handlers.

Specific immunotherapy is readily available in Australia to reduce the risk of anaphylaxis to bees and some wasps and, in some states (Tasmania, South Australia and Victoria), to jack jumper ants (JJAs). The accepted term now is venom immunotherapy – it does not 'reverse' anaphylaxis but reduces the risk of anaphylaxis to future envenomation events.

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What is allergy?

A simple definition of allergy is an adverse immediate specific immune response to an external substance. In this context, it is typically abrupt, explosive and brief. Such immediate generalised (allergic) reactions (IGR) begin within 30 to 60 minutes (sometimes in 30 seconds) of exposure and may involve multiple systems in rapid progression. If the patient survives the insult, the reaction will usually ease in a few hours.

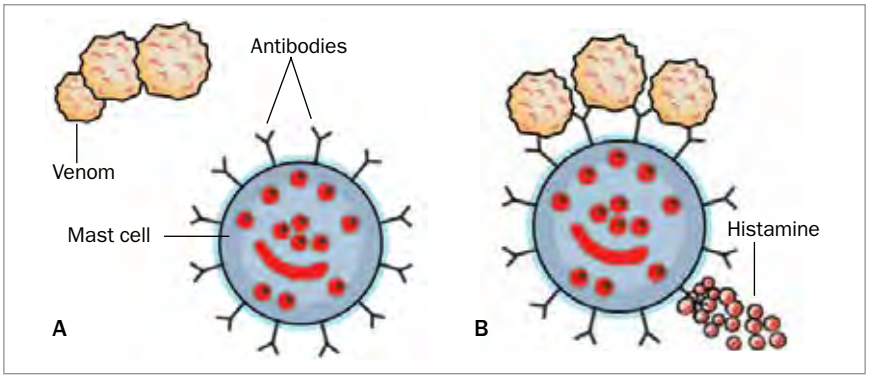
How common is allergy to stings and bites?

Allergic reactions to stings and bites from insects and ticks result in a significant degree of morbidity in the community. Overseas experience indicates that the prevalence of life-threatening stinging insect allergy ranges from 0.5 to 7%.[1-3] In Australia, almost 5% of the Tasmanian population have had an IGR to a sting, while 6.5% of South Australians self-reported a history of systemic reaction to insect sting.[4,5] In South Australia, Tasmania and Western Australia there are 7.5 to 10.6 hospitalisations per 100,000 people per annum as a result of bee stings alone, but the figures in the other states are much lower.[6-8]

Australian records show that at least one or two people die each year from either bee, wasp or ant stings.[7,9] Deaths from tick allergy have also occurred.[7] Deaths are likely to be substantially underestimated because of under-reporting, frequently unwitnessed occurrences of stings and bites and poor sensitivity of autopsy for anaphylaxis.[10,11]

Who is likely to be allergic to insect stings or bites?

Allergic reactions are determined by genetics and exposure. As a rule, an individual patient will react only to a particular insect species; that is, a patient who has had a severe reaction to a bee sting is most unlikely to react similarly to a wasp sting. An exception to this is that there is significant cross-reactivity between different vespid (wasp and hornet) species. Furthermore, it is almost impossible to experience an allergic response to the first sting from a particular insect. Thus, the patient undergoes a priming or sensitising period in which he or she tolerates one or more stings but is primed to react to a subsequent sting from that species (Figures 1a and b).[12]



Figures 1a and b. Mechanism of the allergic response to venom. a (left). An antibody response is triggered by the presence of venom in the body and these antibodies attach to the mast cells. b (right). When venom comes into contact with the antibodies, the mast cells respond by releasing substances such as histamine, which cause swelling and inflammation.[12]

Adapted with permission from Marion Merrell Dow.

Species responsible for allergic reactions

All the stinging insects belong to the order Hymenoptera. Allergic reactions occur to the venoms these insects produce. Insects whose stings may cause allergic reactions include:

- European honey bees (*Apis mellifera*)
- paper wasps with paper nests (*Polistes and Ropalidia* spp.)
- wasps with mud nests (*Sceliphron* sp.)
- hornets (*Vespa* sp. – true hornets), which are not established in Australia
- European wasps, which usually have nests in the ground (*Vespula germanica* and, in Victoria, *Vespula vulgaris*)
- Australian ant species: JJAs (*Myrmecia pilosula*), other bull/inch ants (about 90 species of predominantly larger *Myrmecia*), greenhead ants (*Rhytidoponera metallica*) and others[13]
- the red imported fire ant (*Solenopsis invicta*) – first recorded in Queensland and targeted for eradication.

The March fly (family Tabanindae) and the paralysis tick (*Ixodes holocyclus*; an arachnid) are biting (rather than stinging) insects which produce salivary proteins that can cause allergic reactions.

Types of reactions

Responses to insect stings and tick bites vary widely.

Sensitisation

It must be recognised that far more people are sensitised with specific IgE antibodies to the venoms of prevailing Hymenoptera species than have had or will have systemic reactions to stings from these same species (Figure 2).[14-16]

Clinical reactions

There are four primary categories of clinical reactions to stings and bites from insects and ticks.

Normal response

A normal response to an insect sting or tick bite is characterised by a burning or painful wheal up to several centimetres in diameter

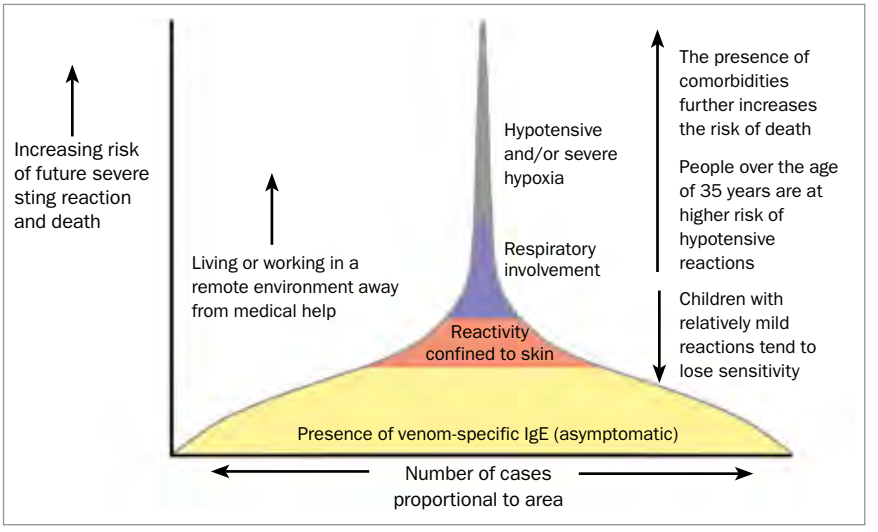


Figure 2. Level of risk versus population prevalence of sensitisation and insect sting reaction history.[14]

Figure 3. *Apis mellifera* (the honey bee). The presence of a retained stinger in the skin is diagnostic. In very hot weather honey bees seek out water and may be encountered accidentally in open drink bottles (leading to oropharyngeal stings and airway obstruction).

confined to the sting or bite site. It usually resolves in a few hours or days.

Large local swellings

A large local swelling may develop from the sting site and may vary enormously in extent. A sting on the hand, for example, may result in swelling of the entire hand or extend to the elbow, or even to the shoulder or neck. The durations of these reactions vary widely, some resolve within hours, whereas others persist for many days. These reactions may be toxic or allergic, and evolve within 30 minutes or may take up to 24 hours. Allergy-induced large local swellings may develop rapidly and are mediated by the specific antivenom allergic antibody.[16]

Minor IGR

A minor systemic response involves parts of the body distant from the sting site but without clinically significant cardiovascular or respiratory involvement. The most common manifestation is a reaction confined to the skin (generalised urticaria and/or facial angioedema). Gastrointestinal symptoms are often seen in patients with evolving hypotension, and should not be regarded as mild symptoms in the context of a sting or bite.[17]

Major IGR/anaphylaxis

In a major systemic response, body organs vital to life (i.e. the respiratory or cardiovascular systems) are impaired by the anaphylactic response. A common response is that within a few minutes of being stung or bitten (e.g. on the arm), the patient may develop facial pruritus or flushing. This is followed quickly by pruritus and then frank urticaria elsewhere on the body. The patient may develop gastrointestinal symptoms or become extremely apprehensive with a sense of imminent death, feel so weak that he or she cannot stand, may lose vision, collapse, become unconscious and/or dyspnoeic, with a choking sensation or chest tightness, or even all of the above. Some patients may develop acute hypotension with collapse or dyspnoea without a rash or swellings. Uterine cramping, which may be the dominant complaint, can be as severe as labour pain.

Risk of a major response

As a general rule, each individual has a unique way of responding to a sting or bite. Therefore, if a minor systemic response has occurred, a subsequent sting or bite will most likely result in a similar reaction.[4,16,18] Occasionally, patients may progress from a large local swelling to a minor systemic event or even a major response. Stings on the head or neck do not necessarily put a patient at a higher risk of a major reaction than stings occurring on lower parts of the body, although one study reported a higher rate of systemic reactions in patients who had been stung on the neck or trunk.[19,20]

As indicated in Figure 2, patients who have never had an adverse response have a low risk of experiencing a future IGR.[14] Those with a history of large local reactions have a risk of experiencing a future IGR of about 5 to 10%, whereas those who have had systemic reactions to bees or wasps limited to the skin have up to a 20% risk (lower in children). Many of these IGRs will be minor. However, patients who have already had an anaphylactic reaction to a sting have a 40 to 60% chance of reacting the same way to any future sting from the same species, whereas in JJA allergy it is consistently around 70%.[4,16]

Rarely, patients may experience serum sickness, a neurological reaction or vasculitis. Occasionally, a patient may have a major systemic reaction after being stung by many insects at the one time. Some may be toxic events but in the absence of allergy, healthy adults can tolerate vast

Figure 4. *Vespula germanica* (the 'European wasp' or 'yellow jacket') is found mainly in cooler regions. It is characterised by a waist part that becomes rapidly thicker at the abdomen and by its way of holding its legs close to the body during flight. These insects are particularly attracted to rotting meat, fallen fruit and sweet drinks (leading to oropharyngeal stings and airway obstruction).

numbers of stings and many of these reactions appear to be allergic.[19] Thus, this group has a high risk of anaphylaxis if re-stung by a single insect from the same species.

Reactions to insect and arachnid stings and bites

European honey bees

Hospitalisations and deaths due to stings from honey bees (*A. mellifera*; Figure 3) occur disproportionately in 'western climates' of Australia, specifically in Western Australia and South Australia.[6-8,10] Immediate systemic reactions to honey bee stings do not peak in spring as expected but with high maximum temperatures.[21]

Wasps

Australia has numerous species of paper wasps. They are prevalent in the northern half of the continent. Clinical experience indicates that some patients show allergic reactivity to only certain species of wasps. The two major species in Australia are: *Polistes*, which build a rosette type of nest, and *Ropalidia*, which build a nest of two long columns. Diagnostic problems arise because the only available test and immunotherapy reagents come from the USA and are prepared from the American species of *Polistes*. Thus, about 30% of patients who clearly have had anaphylaxis from wasp stings fail to show positive tests and consequently are not currently candidates for specific immunotherapy.[22] European wasps (predominantly *V. germanica;* Figure 4) are prevalent in cooler urbanised areas of Australia.[14,23]

Ants

Australian ants

Most ants do not sting but Australia, with its uniquely rich ant fauna, has seven genera of ants capable of inflicting sting anaphylaxis. The native *M. pilosula* species complex (JJA, a type of jumper/hopper/skipper ant; Figure 5) appears to be the dominant cause of anaphylaxis in many cooler areas of Australia, with hot spots in Tasmania, southern Victoria and the Adelaide Hills.[4,13,24] In both sting and epidemiological studies, recurrence rates in people with a history of severe generalised reactions have been consistently 70% or more across several studies.[4,25] Multiple deaths have been reported.[26,27] In the hinterland of Sydney and further north in Queensland, a morphologically similar jumping ant with a red thorax (*Myrmecia nigrocincta*) is found. In the far south of Western Australia another type with different coloured hind legs (*Myrmecia ludlowi*) can be found.

Most of the about 90 species of *Myrmecia* might aptly be termed 'inch ants', and they are larger and less aggressive than *M. pilosula* and are often nocturnal (Figure 6). Despite occupying diverse habitats across Australia and some nearby Pacific islands, including one species in New Zealand, these diverse ants are less prominent as causes of anaphylaxis than *M. pilosula*.[13]

The *Myrmecia* diverged from other hymenopterans about 30 million years ago. To date significant cross-reactivity with other stinging hymenopterans has not been demonstrated.

Nothomyrmecia macrops (found rarely in the west of South Australia) appear largely unchanged in fossil records for about 200 million years (personal communication, R. Taylor) and predate many early dinosaurs.

Figure 5. *Myrmecia pilosula* (the jack jumper ant) is a type of 'jumper ant' or 'hopper ant'. About 10 to 12 mm long, it moves in short jerky movements, jumping to attack, sometimes out of surrounding bushes. Serological data suggest that it is responsible for about 90% of ant venom allergy in south-eastern Australia. It has well-developed vision, is attracted to movement and is extremely aggressive.

Figure 6. A variety of larger (15 to 22 mm) *Myrmecia* ants such as *Myrmecia forficata* (known in Tasmania as the 'inchman') are often referred to as 'bull', 'bulldog' or 'inch' ants. Common names can be confusing (some people also refer to jack jumper ants as bull ants), so it is important to record a description of the insect rather than a name. Expert identification is important when a specimen is available because most species are almost impossible to differentiate by the amateur.

Figures 7a and b. *Ixodes holocyclus.* a (left). Adult female, about 3 to 3.5 mm in length. b (right). A semi-engorged nymphal paralysis tick.
Images courtesy of Mr Stephen Doggert.

The red imported fire ant

The red imported fire ant *(S. invicta)* is tiny (2 to 6 mm) and forms huge colonies. It originated from South America and later infested extensive areas of the southern states of the USA. It has been very difficult to eradicate and has caused destruction of farmlands and parks. Many people have incurred anaphylaxis from the stings and there have been fatalities. Red imported fire ant colonies were detected in south-east Queensland in the late 1990s. Eradication programs have been carried out. Two workers in the field developed anaphylaxis early in the program.[28] However, although red imported fire ants have since been detected in New South Wales, Western Australia and (again) Queensland, incursions have been subject to subject to a nationally cost-shared eradication program and efforts to contain red imported fire ant colonies have been reasonably successful.[29]

Ticks

The paralysis tick (*I. holocyclus;* Figures 7a and b) infests almost the entire eastern seaboard of Australia. Anaphylaxis has resulted in many patients, with fatal outcomes in four cases.[30] The most prevalent areas of infestation are the northern beaches of iSydney, the northern rivers of New South Wales and the hinterland of southern Queensland. The tick embeds its mouth parts in the skin and the allergic reaction occurs when the tick is disturbed in situ (i.e. if it is pulled out or even if it is scratched), which causes release of more saliva.

Red meat allergy is quite rare but it has been described relatively commonly in people who have had previous tick bites, possibly even in those who have not had an adverse event. Further studies have shown that the tick's saliva contains a carbohydrate, galactose-alpha-1,3-galactose (alpha-gal), that is found in almost all mammalian meats. This is a unique allergen because all other allergens are proteins.[31,32]

Diagnosis

Identification of the offending insect

Identification of the inciting insect needs to take account of the geographical location, circumstances of the sting and observations made at the time. Honey bees leave a 'stinger', which is not a feature of wasps or ants recorded in Australia. European wasps have ground nests and are attracted to sweet foods, so a person may be stung at a picnic by a wasp in a soft drink. Jumper ants have a very characteristic appearance, movement and aggression and can sting through even thick textiles. March flies typically stay at the site. Ticks are embedded in the skin.

Assessment of reaction severity

Assessment of the severity of the reaction should take account of the history and any objective observations, particularly vital signs after the event. Note that patients may recover spontaneously and that observations made on arrival at care may underestimate peak reaction severity. Alternatively, objective observations may show that a reaction was far more serious than the history would suggest.

Confirmatory objective tests

There are two types of tests to confirm an allergic reaction:

- in vivo skin tests
- in vitro serological tests for specific venom IgE antibodies.

In vitro tests are available only for the specific venoms of honey bees, some paper wasps, European wasps and *M. pilosula* (through SA Pathology) but not for the salivary allergens of March flies or ticks. The preponderance of asymptomatic sensitisation relative to clinical reactivity means that the testing of patients with no history of a systemic allergic reaction will result in many positives with very poor positive predictive ability for clinical reactivity.

If doubt exists as to the causative insect, serological testing for venoms of as many as possible of the locally prevalent insects should be performed. However, the level of reactivity on skin or in vitro testing does not predict the severity of the clinical reaction.[16]

Skin tests

Specific venom extracts from bees and wasps, not whole-body extracts, must be used. They are available as freeze-dried powders and reconstituted with a diluent of albumin-buffered saline.

Testing for allergy to the venom of the *M. pilosula* species complex is the same as for bees and wasps. However, it is only available under special conditions requiring TGA, local hospital and Royal Hobart Hospital Pharmacy approval.

Testing is preferably deferred for two weeks after an anaphylactic event because some patients have a short refractory period in which allergen-specific antibodies may not be detected.[33]

Venom skin testing requires expertise in terms of venom selection, performance and interpretation, and intradermal tests carry a risk of anaphylaxis. Although the risk of anaphylaxis is relatively low, testing should be performed by practitioners experienced in these areas and who are prepared to manage anaphylaxis, whether to the testing venom or subsequent venom immunotherapy.

In patients with severe clinical reactions, the initial test may be a skin prick test at 1.0 mcg/mL. If this is negative, intradermal testing should be performed, starting at 0.01 mcg/mL. If negative, further testing should be performed at 15-minute intervals using increasing concentrations (0.1 and finally 1.0 mcg/mL) until a positive response is found.

In vitro tests for specific IgE

In vitro tests for specific IgE (previously called RAST tests) detect unbound venom-specific IgE antibody in serum. There is generally a close correlation between skin test reactivity and circulating allergen-specific IgE, but discordant results may occur.

Positive results with poor correlation and clinical reactivity to vespid and honey bee venoms may occur in atopic patients with high total IgE levels from IgE antibodies to common carbohydrate found widely in plant materials, including pollen, as well as in bee and wasp venoms. If such a result is suspected, an immunology laboratory should be contacted for advice on further testing using recombinant allergens.

False-negative results also occur in both skin testing and in vitro tests, especially with wasp venoms. A patient who is negative in one test should be assessed by the other test and the test repeated one to two months later before being declared 'negative'.[33] If the tick-associated red meat allergy is suspected, a serological test for alpha-gal is usually positive.

Other tests for sting anaphylaxis

Mast cell tryptase

Mast cell tryptase, a relatively stable product of mast cells, is released at a steady rate and maintains a stable serum level throughout life unless there is widespread mast cell activation or a mast cell disorder. The level rises within 15 to 30 minutes of onset of a major systemic allergic reaction and typically remains elevated for about eight hours. However, failure of elevation does not exclude anaphylaxis (especially in food allergy).

The sensitivity and specificity of testing is increased by comparing the acute level with a convalescent level as increases of at least 20% over the individual baseline and at least 2 ng/mL (absolute value) appear to be a sensitive and specific marker for sting anaphylaxis.[34,35] If the baseline tryptase level is raised and irrespective of whether classical urticaria pigmentosa is present, a mast cell disorder may be present, representing a special risk factor for sting anaphylaxis.[36-38]

Sting challenges

Sting challenges carry a significant risk of anaphylaxis and can give false-negative results, in part because venom delivery is highly variable.[39] They are not recommended in routine practice.[33]

Minimisation of risk of envenomation

To minimise the risk of being stung or bitten by insects or ticks, people should:

- be aware of likely circumstances and localities of insects or ticks concerned
- maximise clothing protection
- avoid provoking insects or ticks.

Honey bees

People should be aware of the likely presence of honey bees, especially around water in hot dry conditions. If stung the stinger should be flicked out as soon as possible. If left in situ, the venom sac will deliver 90% of its contents within 30 seconds.[39]

Wasps

People should be aware of the presence and attraction of European wasps to food and sweet drinks. Some areas have effective *Vespula* control programs.

M. pilosula species

It is more difficult to protect against stings of *M. pilosula*, which is highly aggressive, able to leap from vegetation to humans and can sting through thick textiles. Moving is an option if a suitable area free of JJAs can be found but in South Australia this insect is being found in previously unsuspected locations. Although it is a protected native insect essential to pollination of some native orchids (*Leporella fimbriata*), insecticide treatment of nests close to homes is often chosen as a way of reducing the risk of being stung.

Ticks

Tick-infested areas should be avoided. If time is spent in these areas, clothing should be removed and placed in a hot dryer. Careful searches of the body, especially the scalp, should be performed because ticks may take up to two hours to attach. Some insect repellents containing N,N-diethyl-meta-toluamide (DEET) may discourage ticks.

If a tick is found embedded in the skin it should not be disturbed. Ideally it should not even be scratched, which of course may be difficult to do. It must not be pulled out, because forcible extraction causes more saliva to be released into the skin. The most effective method of reducing the risk of an allergic reaction is to kill it in situ. Ether has been shown to kill ticks rapidly.

Furthermore, once dead the tick will desiccate and may fall out by itself or can be easily scraped out with a credit card or a blunt knife without a reaction occurring. Products containing ether, including Aerostart, which is well known to mechanics, and sprays containing dimethyl ether used to freeze warts are recommended.

MANAGING SEVERE ALLERGIC REACTIONS[43]

- Lay the patient flat on their back
  - if unconscious, place in recovery position (on left side if pregnant)
  - if breathing is difficult, allow them to sit with legs outstretched
  - hold young children flat, not upright
- Give intramuscular adrenaline into the anterolateral thigh
- Call for help (ambulance and family or emergency contact)
- If there is no response after five minutes, further adrenaline may be given
- Once in hospital, the patient should stay for at least four hours of observation
- IF IN DOUBT GIVE ADRENALINE AUTOINJECTOR
- Start CPR at any time if person is unresponsive and not breathing normally

Treatment

Large local swellings

Large local swellings represent very intensive inflammatory events. Oral antihistamines and topical corticosteroids are often ineffective. An oral NSAID or single dose of oral corticosteroid will usually suppress the reaction rapidly.

Minor systemic reactions

An oral antihistamine should be sufficient for minor systemic reactions. It should be noted that this will not prevent a major systemic response.[40]

Rapid-onset systemic reactions

First aid treatment

First aid treatment of rapid-onset systemic reactions has been revolutionised by the ready availability of automated adrenaline injectors designed for lay use. Adrenaline is the only medication shown to work rapidly after onset of a systemic reaction.[40,41] Even in patients with stable vascular disease, the risks of a small intramuscular dose of adrenaline through an automated adrenaline injector are likely to be far less stressful than hypotension and/or hypoxia.

All patients with a history of a rapid-onset systemic reaction to a sting or bite should have an automated adrenaline injector and an action plan (plans and e-training are available at www.allergy.org.au). In controlled sting studies, hypotension is the most common serious outcome.[41,42]

A patient experiencing anaphylaxis should be kept supine or supine with legs raised, and allowed to sit if breathless, but not allowed to stand.[11,40] Once the autoinjector has been used, an ambulance should be called. After stabilisation following anaphylaxis, the patient should be held for medical observation so that appropriate treatment can be given if the reaction re-emerges as the effect of adrenaline diminishes. Rural patients need a prearranged plan for linking to emergency services.

Medical treatment

For an excellent practical review of the management of anaphylaxis, readers are referred to the Australasian Society of Clinical Immunology and Allergy (ASCIA) action plans for anaphylaxis (https://www.allergy.org.au/hp/anaphylaxis/ascia-action-plan-for-anaphylaxis). Key measures are summarised in the Box.[43] Intramuscular adrenaline into the anterolateral thigh gives peak levels within a few minutes more reliably than subcutaneous administration.[40] Intravenous adrenaline by infusion is a procedure that should only be performed by those with high-level resuscitative skills. In patients with hypotension, posture and fluid resuscitation with normal saline is important as massive fluid losses can occur in anaphylaxis through both redistribution and extravasation of fluid from the vascular system.[32] Patients who have had a major reaction should be held for at least four hours after stabilisation and the last dose of adrenaline, in order that any re-emergent reaction can be dealt with appropriately. A patient who has required adrenaline to treat a reaction or who has been assessed by a clinical immunologist or allergist, respiratory physician or paediatrician as at risk of further anaphylaxis qualifies for a PBS-subsidised automated adrenaline injector, which must be given with an action plan. Medic Alert bracelets should be considered.

Venom immunotherapy

Risk assessment

Venom immunotherapy is a long-term treatment requiring a significant commitment of time and having a significant comorbidity. Therefore, a careful assessment needs to occur.[1] The risk of an anaphylactic reaction to a further sting can be estimated (Figure 2). Any adult with a history of an IGR, even if confined to the skin, and any child with a history of anaphylaxis should be considered at high risk of serious reaction to a future sting from that species.[2] Exposure level and geographic location must be considered.[4]

Comorbidities and their treatments need careful assessment because there are several that may add to the risk of adverse outcomes from a further sting and to the potential difficulties of venom immunotherapy. Although signalling a need for caution and often expert assessment of the comorbidity and its treatment, such comorbidities add to the case for venom immunotherapy in expert hands because the risks of graded doses of venom given in carefully controlled conditions are likely to be substantially less than a sting away from medical care.[36]

Comorbidities thought to contribute to risk are mast cell disorders, often presenting as hypotension without rash, disorders that involve vascular or respiratory compromise.[36,38] The use of some antihypertensives (such as beta-blockers and ACE inhibitors) is no longer considered a generic risk factor for more frequent or severe anaphylaxis to venom stings or immunotherapy, although whether they still pose a risk for specific individuals is subject to debate.[36-38,44,45] Judgement and often co-management are required in assessing the risk and benefit of, and alternatives to, these agents.

Giving venom immunotherapy

The principle of venom immunotherapy is that by giving carefully graded doses of the relevant venom subcutaneously, clinical reactivity is greatly reduced. Diverse mechanisms account for this effect, which is venom specific, but controlled studies have involved honey bees, wasps and JJAs. Trials of venom immunotherapy with honey bee, vespid or JJA venom leave no doubt that such therapy is effective in reducing (by about 90%) the probability of having a rapid-onset systemic allergic reaction to another sting from the same species.[25,46,47] Even the 'failures' are almost always milder than the index reaction.[47] The specificity of the therapy, morbidity (including risks of anaphylaxis, especially with the more convenient accelerated regimens and venom type) and duration of therapy required for long-term benefit mean that such therapy should be selected, initiated and guided by a trained allergist or clinical immunologist.[37,48]

Adults who have experienced rapid-onset generalised allergic reaction, even if confined to the skin, and children who have had such a reaction extending beyond the skin qualify for venom immunotherapy, provided that there is evidence of specific IgE (by venom skin testing or in vitro testing) to the relevant available venom and informed consent acknowledging the duration and side effects of the therapy. In general, children with reactions limited to the skin and adults with large local reactions or asymptomatic sensitisation do not qualify for therapy because the risk of future anaphylaxis to sting in such patients is small (<10%; Figure 2).[14]

Until maintenance doses of venom are reached, venom immunotherapy carries a risk of rapid-onset allergic reactions sufficient that a specialist most appropriately carries this out. The risk varies with insect venom, being higher for honey bees, paper wasps and JJAs than 'European' wasps (*Vespula* sp.), and with regimen. It is nevertheless always significant.[25,37,47,49]

Stopping venom immunotherapy is problematic. Patients who have tolerated five years of maintenance venom immunotherapy without systemic adverse reaction appear to have protection that usually persists for many years, even when some IgE to venom remains detectable. However, it has been estimated that after stopping venom immunotherapy, there is about a 10% chance of loss of protection with each subsequent sting.[16] Patients who have experienced reactions that were life-threatening with hypotension and/or hypoxia (rather than reactions that might have evolved to that stage), cardiorespiratory compromise at baseline, a mast cell disorder, frequent stings or redevelopment of allergy following a previous adequate-duration course of venom immunotherapy should be continued on indefinite venom immunotherapy. Clearly, the decision to stop venom immunotherapy is nuanced, and should involve the clinical immunologist or allergist.

Honey bee and European and paper wasp extracts are available through the PBS. JJA venom is only available under special conditions requiring TGA, local hospital and Royal Hobart Hospital Pharmacy approval (contact Jenny Gudden, Operations Manager, Jack Jumper Ant Allergy Program, Royal Hobart Hospital). JJA venom immunotherapy in Australia and red imported fire ant venom immunotherapy in North America are the only ant allergies with established desensitisation treatment protocols. There are no March fly or tick extracts available for immunotherapy.

Conclusion

Anaphylactic events are common. In some, the cause may be obscure; thus stinging insects and ticks should be considered among the many possible causes. A careful history must be taken and if insect or tick allergy is likely, it would be useful to do a preliminary serological test for allergy to the specific venom. If the patient has experienced a systemic reaction, a major or minor, and even if the blood test is negative, a referral to an allergist or immunologist is necessary. In addition, an automated adrenaline injector and action plan should be promptly provided on an authority prescription. Patients should be made aware that it is possible in some cases to suppress the allergy by specific venom immunotherapy. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Beware of allergic reactions to stings and bites

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Adrenaline injectors

Update on prescribing

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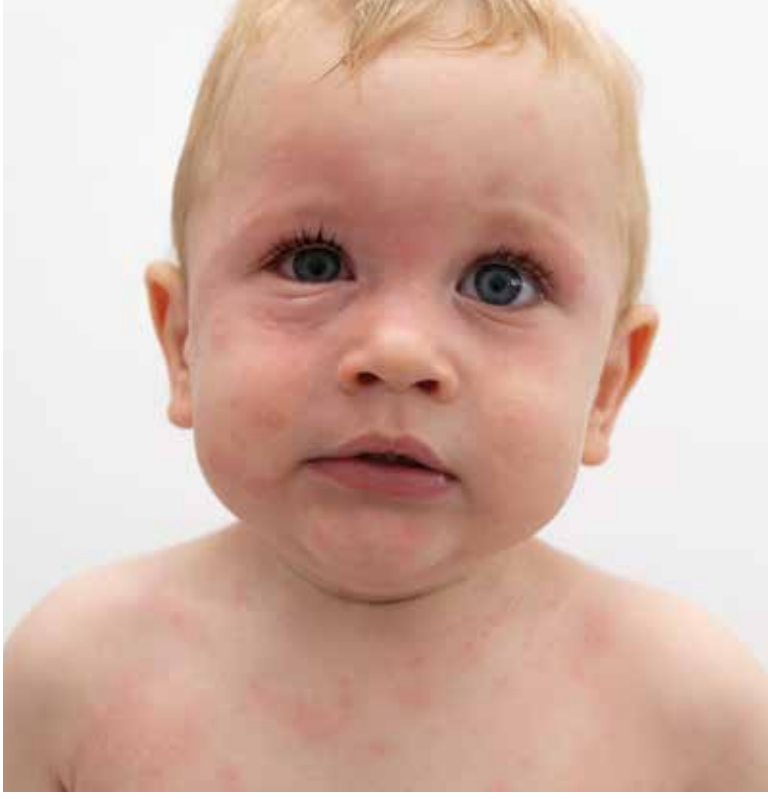

Adrenaline (epinephrine) is the first-line treatment for anaphylaxis, and two types of adrenaline injector are available for use in Australia. Prescribers need to be aware of the different instructions for their use and recent changes to adrenaline dose recommendations.

Anaphylaxis is a severe, potentially life-threatening allergic reaction, and intramuscular (IM) adrenaline (epinephrine) is the treatment of choice.[1-4] Adrenaline injectors (AI) have been available for more than 40 years and allow rapid administration of IM adrenaline by the patient or a lay person.[5-7] In Australia, the EpiPen AI has been available on the PBS since 2003. From 2021, a second type of AI device that can deliver a higher dose is also available on the PBS, Anapen. Here, we discuss the role of AIs in treating anaphylaxis, how to prescribe them, including dose and patient education, and compare EpiPen and Anapen.

What are adrenaline injector devices?

AIs are single-use devices that deliver a set dose of adrenaline, designed for use by people without medical training to treat anaphylaxis. Adrenaline is the only first-line drug to treat anaphylaxis and should be administered promptly by IM injection into the outer mid-thigh.[1-3] IM administration has been the route of choice for optimal delivery of adrenaline in treating anaphylaxis for over 20 years.[1,3,4,8] There are no contraindications to the use of IM adrenaline to treat anaphylaxis.[2,4]

Adrenaline is a nonselective adrenergic agonist with a rapid onset of action. Adrenaline acts to reduce airway mucosal oedema, induce bronchodilation, induce vasoconstriction and increase cardiac contraction strength.[1,4] Two AI devices are TGA approved and available in Australia, with both listed on the PBS: Anapen (containing 150, 300 or 500 mcg doses) and EpiPen (containing 150 or 300 mcg doses). A generic AI similar to EpiPen is also PBS listed. AIs are designed to keep adrenaline stable and have an expiry date in excess of one year after manufacture.

When to use an AI device

AIs are used for the first-line treatment of anaphylaxis. Anaphylaxis is a severe allergic reaction that is often under-recognised and undertreated.[1,3,9] Definitions vary worldwide, but the Australasian Society of Clinical Immunology and Allergy (ASCIA) defines anaphylaxis as:[2]

- 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 (gastrointestinal symptoms of any severity are a symptom of anaphylaxis to insect stings or injected drugs); or
- any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.

The ASCIA definition is consistent with the criteria published in the *World Allergy Organization (WAO) Anaphylaxis Guidance 2020*.[3]

AIs may be self-administered or given by people without medical training. AIs are also sometimes used to treat anaphylaxis in medical facilities as they contain a fixed dose of adrenaline, which may reduce the risk of overdose and delays in administration.

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Although most anaphylactic reactions are not fatal, reactions are unpredictable.[10,11] Factors that may affect the severity of reactions include dose of the allergen, route of exposure, presence of asthma, other drug use (alcohol, beta blockers, ACE inhibitors) and exercise, but importantly, there are no reliable clinical predicators of a severe reaction.[3,4,10] Although patients who have previously had anaphylaxis would be considered at risk of subsequent severe reactions, a history of previously mild reactions is not a good predictor of subsequent reaction severity.[10,12] Early use of IM adrenaline can treat the symptoms of anaphylaxis and reduce the risk of fatal reactions, although these sometimes still occur.[1,3,4,12,13]

Antihistamines and corticosteroids do not treat or prevent anaphylaxis and should not be used in the first-line treatment of anaphylaxis.[1,10] Patients may fear adrenaline or feel reassured that past reactions with respiratory or cardiovascular symptoms have resolved either without treatment or with the use of antihistamines or corticosteroids. However, any apparent benefit is not due to the action of either medication, whose onset and mechanisms of action will not reverse symptoms of anaphylaxis, but due to endogenous responses, which may vary with each reaction.[1,4,10] Although antihistamines are listed on the ASCIA action plans to treat mild to moderate symptoms of allergic reactions such as hives, progression to respiratory or cardiovascular symptoms should be treated with an AI without delay.

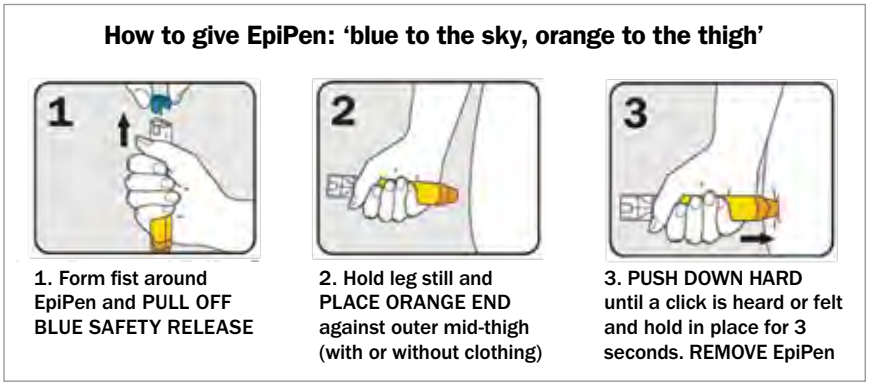

Figure 1. Instructions for giving EpiPen.
Reproduced with permission from Australasian Society of Clinical Immunology and Allergy (ASCIA).

How to give AI devices

Instructions on how to administer adrenaline with EpiPen and Anapen are shown in Figures 1 and 2, respectively. Instructions and videos are also available on the websites of ASCIA (https://allergy.org.au/) and the patient support organisation Allergy and Anaphylaxis Australia (https://allergyfacts.org.au).

Features of Anapen and EpiPen are compared in Table 1. Patient cost is the same as both are subsidised by the PBS and they have similar over-the-counter prices.

Prescribing AI devices

AI devices are available in Australia on PBS authority prescription, and an initial prescription is indicated for the anticipated treatment of anaphylaxis. This can be prescribed by a clinical immunologist or allergy specialist, paediatrician or respiratory physician, or by a doctor or nurse practitioner if the patient has been discharged from hospital or an emergency department after treatment with adrenaline for anaphylaxis. Because of different legislation, emergency physicians in NSW are unable to prescribe AI on authority prescription, but it is recommended that the patient is provided with at least one AI by the hospital pharmacy on discharge.

Sometimes, patients who have had a clear episode of anaphylaxis do not receive adrenaline in the emergency department for a range of reasons, including failure to present, symptom improvement by the time they arrive in the emergency department, or failure of treating staff to

Figure 2. Instructions for giving Anapen.
Reproduced with permission from Australasian Society of Clinical Immunology and Allergy (ASCIA).

TABLE 1. COMPARISON OF ADRENALINE INJECTORS

Feature	Anapen	EpiPen
Injection site	Designed to be placed on the outer mid-thigh before injection; the needle is not visible before activation	
Needle length	10.5 mm*	15.5 mm (with 5 mm variation)*
Administration technique	• Anapen activates when you apply light pressure while pressing the red button on the top of the device • Hold in place for 10 seconds	• EpiPen requires you to apply pressure to activate the device by pushing into the thigh with the device • Hold in place for 3 seconds
After use	The Anapen needle remains exposed after injection. To prevent needlestick injuries, place the needle into the wide end of the black needle shield, or place the used Anapen in a container	EpiPen has a needle shield that covers the needle as the device is lifted off the thigh
Disposal	After use, the device should be given to the attending ambulance along with a report of the time it was given	

* Compared with an average needle length of 25.4 to 33.5 mm used for intramuscular injections.[5]

recognise anaphylaxis. In these cases, GPs (and emergency department medical officers) have the option to contact an on-call hospital immunologist to discuss authorisation for an initial AI prescription, given the PBS criteria state that the patient 'must have been assessed to be at significant risk of anaphylaxis by, or in consultation with, a clinical immunologist'. This can prevent a possible excessive delay for AI prescription, given the potentially long wait time to see an immunologist or other specialist.

Patients are eligible for up to two devices per prescription with no repeats. Continuing PBS supply for anticipated treatment of anaphylaxis can be prescribed by a doctor or nurse practitioner if the patient has previously been issued with an authority prescription and their devices have been used or expired. It is important to specify the brand and tick the 'no substitution' box on a PBS prescription to ensure the brand is not substituted. AIs are also available without prescription at a nonsubsidised cost.

Prescribing an AI alone is not enough to manage patients at risk of anaphylaxis. It is important also to provide education on allergen avoidance, recognition of anaphylaxis and AI use, and to encourage patients and families to practise regularly with a training device. Training devices can be reused and are available from Allergy and Anaphylaxis Australia. An ASCIA action plan for anaphylaxis should always be provided with an AI. Anapen- and EpiPen-specific versions are available (https://www.allergy.org.au/hp/anaphylaxis/ascia-action-plan-for-anaphylaxis).

The ASCIA adrenaline injector prescription guide is shown in Box 1.

Adrenaline dose

The optimal dose of adrenaline to treat anaphylaxis is not known.[5-7] Current recommendations are based on limited pharmacokinetic studies in healthy people but are supported by decades of clinical practice.[1,3-7]

In line with international guidelines, ASCIA recommends an adrenaline dose of 0.01 mg/kg (maximum 0.5 mg) to treat anaphylaxis (Table 2).[1,3,4] IM adrenaline should be given at a dose of 0.01 mL/kg of a 1:1000 (1 mg/mL) solution, as this gives acceptable volumes for IM injection.

For adrenaline IM autoinjection, ASCIA recommends a 150 mcg AI device for patients weighing between 7.5 and 20 kg, a 300 mcg device for patients weighing between 20 kg and 50 kg, and a 300 mcg or 500 mcg device for patients weighing 50 kg or more.

ASCIA's weight recommendations differ from those in the product information for both the Anapen and EpiPen AIs. In 2021, ASCIA revised the lower limit of its weight recommendation for the 150 mcg AI device from 10 kg to 7.5 kg, based on the following rationale.

- The change aimed to reduce potential underdosing and provide AI options for infants weighing less than 10 kg. Food allergy is prevalent in this age group, and prescribing adrenaline to those at risk of anaphylaxis is challenging.[7,10] Currently, a 100 mcg AI is not available in Australia. The options are either to provide an ampoule of adrenaline with a sterile syringe or a prefilled syringe or to prescribe a 150 mcg AI.
- Although the use of a 150 mcg AI delivers double the recommended 0.01 mg/kg dose in a 7.5 kg infant, IM adrenaline has a good safety profile and is generally well tolerated.[7,12,14]
- Providing a syringe and ampoule of adrenaline to parents is strongly discouraged as it increases the risk of significant dosing errors (as a high as 40-fold in one study) and leads to delays in administration.[15]
- Providing a pre-filled syringe of adrenaline also has disadvantages as a method to prevent the plunger being depressed is not easy to achieve, and the syringe needs to be refilled regularly as adrenaline is stable in a syringe for only up to three months.[7]

The recommended dose of adrenaline for adults weighing 50 kg or over is 0.5 mg.[1-4] Although either a 300 mcg or 500 mcg AI can be used in teenagers and adults, a 500 mcg device gives a higher maximum concentration of adrenaline. A person weighing 50 kg would receive

almost 50% less than the recommended dose with a 300 mcg device.[6,7] Adrenaline generally reaches its peak concentration five to 10 minutes after injection by AI, so if anaphylaxis symptoms persist at five minutes then a second dose is recommended.[2,3,5,6]

Concerns have also been raised about the potential for subcutaneous injection with AIs in people with a greater skin-to-muscle distance. Although larger head-to-head studies of AIs are needed, a recent systematic review concluded that device-dependent injection force and speed may be more important than needle length in determining adrenaline pharmacokinetics, and that the time to peak adrenaline concentration was generally longer in people with a greater skin-to-muscle distance, although overall bioavailability was similar.[6,16]

Why are there two AI devices available in Australia?

Since 1 September 2021, two AI devices have been available in Australia on the PBS. Most countries have multiple brands of adrenaline injector devices available, and both EpiPen and Anapen devices are widely used in other countries. Having both EpiPen and Anapen available is important:

- to ensure continued supply of life saving adrenaline, particularly if one brand has stock shortages
- to provide doctors with a choice of dose as
  - they may prefer to prescribe a higher dose (500 mcg device) for people who weigh over 50 kg
  - a 500 mcg dose may potentially prevent the need for further doses of adrenaline (which is important due to increasing ambulance delays and many people carrying only one device)
- to encourage suppliers to provide devices with longer shelf life
- to provide choice for consumers to access devices with points of difference to best suit their needs.

1. ASCIA ADRENALINE INJECTOR PRESCRIPTION GUIDE[2]

Adrenaline injector prescription is recommended for patients with:

- history of anaphylaxis, if the patient is considered to be at continuing risk from allergic reactions to identified triggers (confirmed allergen/s) or unidentified triggers (idiopathic anaphylaxis)
- food allergy (excluding oral allergy syndrome) and coexisting unstable or moderate to severe, persistent asthma. The rationale is that most food allergy-related fatalities occur in people with unstable asthma
- underlying mast cell disorders (e.g. systemic mastocytosis or elevated baseline serum tryptase concentrations) together with any previous systemic allergic reactions to insect stings, including patients undergoing venom immunotherapy

Adrenaline injector prescription is sometimes recommended for patients with a history of a generalised allergic reaction, with one or more of the additional risk factors listed below.

- ***Age***
  - Teenagers and young adults with food allergy. Although food allergy is most common in young children aged 5 years or less, most recorded fatal reactions to foods occur in teenagers and young adults. This may, in part, relate to greater risk-taking behaviour in this age group, but may also reflect the greater likelihood of accidental exposure to food allergens when eating away from home, or while not under parental supervision
- ***Specific allergic triggers***
  - Peanut, tree nuts and seafood. Fatal anaphylaxis may arise from any food, but most fatalities arise from food allergy that persists into adolescence and adult life (e.g. peanut, tree nut, sesame seed and seafood allergies). Allergic reactions to these foods may occur after ingestion of relatively small amounts, and the risk of reaction is unlikely to be reduced by cooking or food processing
  - Generalised urticaria alone without anaphylaxis following insect stings (e.g. bee, wasp or jack jumper ant stings) or following tick bites in selected cases. This condition is not a routine indication for adrenaline injector prescription but may be considered (in conjunction with allergen-specific immunotherapy if available) in selected cases. Decisions regarding immunotherapy will take into consideration factors such as the risk of progression to anaphylaxis (based on follow-up studies), patient age (more likely in adults than children), comorbidity (significant cardiorespiratory disease), living or working in remote areas (where access to emergency medical care may be more problematic), occupational exposure (e.g. bee keeping) or even recreational exposure to stinging insects (e.g. hiking in areas where jack jumper ants are endemic)
- ***Comorbid conditions***
  - Asthma. Unstable or moderate to severe, persistent asthma increases the risk of respiratory compromise in patients with food allergy. Treatment to control asthma symptoms is important in this group (e.g. medication, allergen-immunotherapy)
  - Cardiovascular disease (hypertension, ischaemic heart disease or arrhythmia) is associated with a relatively greater risk of fatal anaphylaxis from insect stings
  - Systemic mastocytosis
- ***Limited access to emergency medical care***
  - Remote residential locations. In some remote residential locations (e.g. remote rural areas), access to medical care and early administration of adrenaline may not be possible unless an adrenaline injector is provided to the patient or their carers for administration. It is important to distinguish this situation of permanent risk from those at short-lived risk (e.g. bushwalking, school camps)
  - Prolonged travel abroad. Consideration of temporary availability to patients who are considered at lower risk but are travelling abroad may also be considered, where language barriers and lesser control over food preparation may increase the risk of accidental exposure, and access to medical care may be limited

This list is not comprehensive and if there is a concern, patients should be referred to a clinical immunology or allergy specialist for assessment.

Abbreviation: ASCIA = Australasian Society of Clinical Immunology and Allergy.

2. PRACTICE POINTS ON ADRENALINE INJECTORS

- Adrenaline (epinephrine) is the only first-line drug to treat anaphylaxis and should be administered promptly by intramuscular (IM) injection into the outer mid-thigh
- Adrenaline injectors (AIs) are devices that deliver a single dose of adrenaline and are designed to be used by people without medical training
- Two AI devices are available in Australia: Anapen (containing 150, 300 or 500 mcg adrenaline) and EpiPen (containing 150 or 300 mcg); both are TGA approved and available on the PBS (up to two devices per prescription) and over the counter
- Prescribing an AI alone is not sufficient to manage patients at risk of anaphylaxis; an AI should be provided as part of a comprehensive management plan including education on how to avoid allergen exposure and how to recognise and treat anaphylaxis
- At the time of AI prescription:
  - tick the 'no brand substitution' box on the PBS prescription to ensure that the brand is not substituted at the pharmacy
  - provide AI training to users as the two devices have different administration techniques, and encourage the use of training devices
  - provide an updated ASCIA action plan for anaphylaxis specific for the AI prescribed

TABLE 2. ASCIA RECOMMENDED ADRENALINE DOSES AND INJECTORS FOR MANAGEMENT OF ANAPHYLAXIS[2]*

Approximate age (years)	Weight (kg)	Volume of adrenaline 1:1000	Adrenaline injector
<1	<7.5	0.10 mL	Not available
1 to 2	10	0.10 mL	150 mcg device for weight 7.5 to 20 kg (under about 5 years)
2 to 3	15	0.15 mL	
4 to 6	20	0.20 mL	
7 to 10	30	0.30 mL	300 mcg device for weight 20 kg and over (over about 5 years)
10 to 12	40	0.40 mL	
>12 and adults	≥50	0.50 mL	300 or 500 mcg device for weight 50 kg and over (over about 12 years)

* Modified from Australasian Society of Clinical Immunology and Allergy.[2]

3. HELPFUL ANAPHYLAXIS RESOURCES FOR HEALTH PROFESSIONALS

Australasian Society of Clinical Immunology and Allergy (ASCIA) (www.allergy.org.au/hp/anaphylaxis)
- Peak professional body for clinical Immunology and allergy specialists in Australia and New Zealand
- Offers a wide range of up-to-date evidence-based online allergy resources including action plans, guidelines, advice and resources for adrenaline injector prescription

Allergy and Anaphylaxis Australia (A&AA) (https://allergyfacts.org.au/)
- National patient support organisation dedicated to helping individuals and carers manage allergy and the risk of anaphylaxis
- Offers an extensive range of online resources and support including videos on how to give Anapen and EpiPen and adrenaline in anaphylaxis

AI complications

AIs are generally safe. Potential injuries related to AI use include injection into a digit, lacerations, embedded needles and bone injury.[7,17] Training can reduce the risk of AI complications, and redesign of AIs over the years has aimed to reduce the risk of injury. Lacerations requiring sutures have been reported in children after AI use.[17] The risk of laceration can be reduced by holding the device in place on the thigh before activating it, and securely holding the child to immobilise the leg and reduce movement.[7,17] Although bone injury is a theoretical risk, particularly in infants and children with shorter skin-to-bone distance, no confirmed bone injuries caused by AIs have been reported.[7,17,18] Bunching the skin before injection may help reduce the risk of bone injury.[7]

How to store an AI

AIs should be stored in a readily available location, in a cool dark place at room temperature (15 to 25°C). AIs should not be kept in a locked cupboard or refrigerated, as temperatures below 15°C may damage the injector mechanism. People at risk of anaphylaxis should have their adrenaline injector with them at all times. An insulated wallet is recommended if a person carrying a device is outside for an extended time, as studies have shown that after even 12 hours in a car on a warm day the concentration of adrenaline in an AI can reduce by up to 14%.[19]

Conclusion

Prescribing an AI is an essential part of the management of people with anaphylaxis. The availability of a second type of AI device adds to the treatment options and can provide a higher adrenaline dose (500 mcg) for people who weigh 50 kg or over. Practice points on AIs are summarised in Box 2 and helpful online resources on anaphylaxis for health professionals are listed in Box 3.

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Adrenaline injectors

Update on prescribing

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