

REVIEW ARTICLE

Insect allergy in children

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Abstract: Allergic reactions to insect bites and stings are common, and the severity of reactions range from local reaction to anaphylaxis. In children, large local reaction to bites and stings is the most common presentation. Stings from insects of the order Hymenoptera (bees, wasps and ants) are the most common cause of insect anaphylaxis; however, the proportion of insect allergic children who develop anaphylaxis to an insect sting is lower than that of insect allergic adults. History is most important in diagnosing anaphylaxis, as laboratory tests can be unreliable. Venom immunotherapy is effective, where suitable allergen extract is available, but is only warranted in children with systemic reactions to insect venom. Large local reactions are at low risk of progression to anaphylaxis on subsequent stings, and hence, venom immunotherapy is not necessary.

Key words: anaphylaxis; immunotherapy; insect allergy.

The patient who presents to the emergency department or to consulting rooms for advice following a possible reaction to an insect bite or sting is a common scenario. Reactions can vary from minor local reactions to anaphylaxis. There are significant regional differences across Australia and world-wide related to insect distribution.

Allergy to bee and wasp venom accounts for most cases of insect anaphylaxis worldwide. Ants are also important causes of insect anaphylaxis, including those from genus *Solenopsis* found predominantly in the USA and genus *Myrmecia* (jack jumper ants (JJA) and bull ants) from Australia. Stings by ant species of the *Pachycondyla* genus are important causes of anaphylaxis in the United Arab Emirates and the far east of Asia. Tick anaphylaxis is an increasingly common problem in many coastal regions of Australia.

Key Points

- Specific venom immunotherapy is indicated in children with a history of systemic reaction involving respiratory, cardiovascular and gastrointestinal symptoms.
- Specific venom immunotherapy is not generally indicated in children with a history of only cutaneous or large local reactions.
- A referral to an immunologist should be made if you suspected a systemic allergic reaction and/or anaphylaxis to insect venom even if the serum specific immunoglobulin E is negative.

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The true incidence of insect anaphylaxis is difficult to establish, as episodes are often are undiagnosed or unrecognised, and therefore under-reported. No specific classification for insect sting anaphylaxis exists in the International Classification of Disease 9 or 10, and this further hinders accurate reporting and data collection. Recent published reviews suggest that anaphylaxis to insect stings makes up 3–34% of adult anaphylaxis cases.¹ In contrast, the incidence of insect anaphylaxis in children is only 0.3–1.0%² of all cases of childhood anaphylaxis. The majority of fatalities occur in middle-aged and older adults, while children tend to more commonly suffer from local reactions and skin symptoms.³

The natural history of insect allergy differs between children and adults. While most adults retain their insect allergy, children have a high resolution rate, with the majority of children outgrowing their insect allergy.⁴ However, up to one in five children whose initial reaction to the sting was systemic in nature (including those with urticaria/angioedema distant to the sting site) will suffer from a systemic reaction if re-stung up to 32 years after the initial sting. In children with initial systemic reactions involving respiratory or cardiovascular symptoms, the risk of subsequent anaphylaxis is estimated to be around 20% justifying venom immunotherapy (VIT) in these individuals.⁴ In contrast, large local reactions (LLRs) tend to decrease with time and the risk of a systemic reaction if re-stung is very low, hence immunotherapy is unnecessary.

Distribution and Behaviours of Stinging Insects in Australia**Bee and wasp**

Honeybees (*Apis mellifera*) and wasps have an Australian-wide distribution.

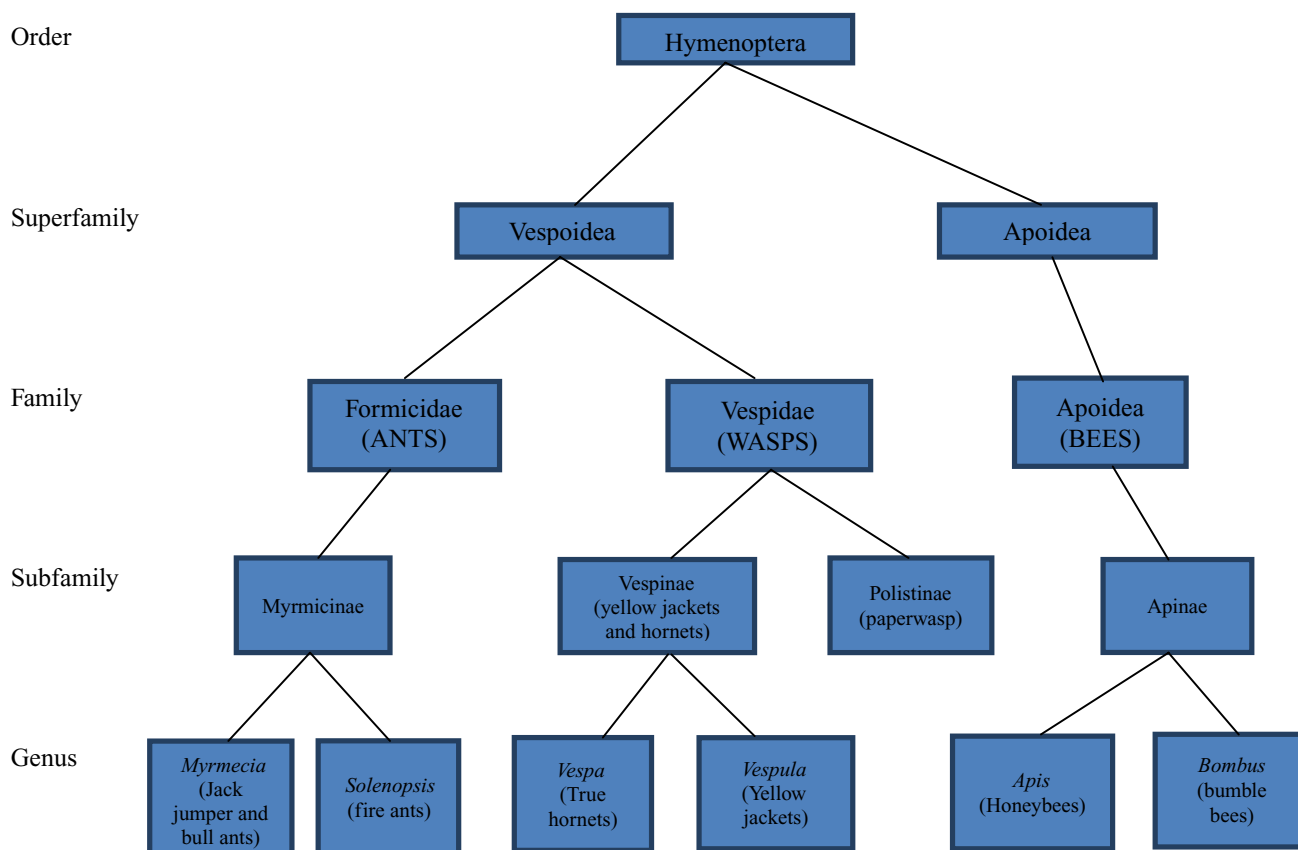


Fig. 1 Stinging insects of the Hymenoptera order: taxonomy tree. Adapted from Up to date 2012.

Yellow jackets, commonly known as the 'European wasps', build their nests on the ground and are often encountered while playing in the garden. Since their introduction into Australia 20 years ago, yellow jackets are now found in every state (Fig. 1).

The common paper wasps build honeycomb nests in shrubs or under the eaves of houses. They are important predators, preying on agricultural and horticultural pests. Yellow jackets are scavengers and are often encountered at outdoor events where food and drinks abound. Domestic honeybees are found in commercial hives, while wild honeybees build their nests in logs or tree hollows.

Ants

Bull ants have an Australian-wide distribution, and JJA are most commonly found in Tasmania but also appear in the Australian Capital Territory, Blue Mountains (New South Wales) and cooler parts of South Australia, Victoria and Queensland. JJA and bull ants are often solitary roamers and do not appear in ant trails. These aggressive ants attack when aggravated. The JJA also has a characteristic of being jerky, jumping action and appearance. Fire ants, which have only been found in Brisbane, build characteristic nests (resembling domes and can grow to 40 cm in height) and often migrate in trails.

The venom from JJA is very allergenic and causes the highest rate of anaphylaxis in the world from a single insect sting/bite. It is estimated that 12 000 Tasmanians and 60 000 Australians will suffer from allergic reactions⁵ from JJA.

Ticks

Ticks are found along the coast of northern and eastern Queensland and New South Wales, parts of Victoria and Tasmania. They are restricted to bush and scrub country as they require humid conditions. Ticks are seasonal and tend to flourish in spring and summer.

Who Suffers from Insect Allergy?

Insect allergy can occur at any age. There may be a history of uneventful past stings. Children tend to suffer from less serious reactions,³ including LLRs and angioedema and urticaria distant to the site of the insect bite/sting. These type of reactions rarely progress to more serious reactions.³

Adults suffer from more serious allergic reactions once sensitisation (exposure to the allergen and specific immunoglobulin E (IgE) production) occurs, with 90% of adult insect allergic



Fig. 2 Distribution of bee, wasp, tick and jack jumper ant in Australia. Map keys are (yellow) bee/wasp, (blue) tick and (green) jack jumper ant.

patients reporting cardio-respiratory symptoms compared with 30% in children.⁴ Once systemic symptoms in adults occur, there is a 25–60% chance of suffering another systemic reaction on a subsequent sting (reviewed in⁶). Subsequent reactions in children tend to mirror the first reaction clinically.³ The risk of a more serious reaction to subsequent stings is small and generally declines with time.^{2,7}

Clinical Features and Diagnosis of Insect Allergy

History

The diagnosis of insect allergy relies heavily on history, as positive tests commonly occur in non-allergic individuals. Twenty to thirty per cent of all adults stung in the previous 3 years have a positive serum-specific anti-venom IgE directed against Hymenoptera venom (bee and wasp),² irrespective of symptoms on sting. A positive test is however useful to confirm an allergy in an individual in the context of a recent convincing allergic reaction. Apart from ticks, most insects' stings/bites are painful, and patients are therefore usually aware that they have been stung or bitten. However, specific insect identification can be difficult and knowledge of the patterns and habits of common insects can be helpful in identifying the likely culprit.

Local and systemic reactions

Local reactions typically cause pain, swelling and erythema. They are confined to the surrounding tissue of the sting site. Local reactions can develop within minutes and gradually increase in size, often peaking at 24–48 h taking 5–10 days to resolve.

Children most commonly suffer from LLRs to insect stings. These LLRs are often clinically indistinguishable from cellulitis and often result in misdiagnosis and unnecessary antibiotic treatment. There is a minimal increased risk of anaphylaxis on subsequent stings; thus, testing and/or immunotherapy is not warranted in children with LLRs.

Skeeter syndrome describes LLRs that are accompanied by lethargy, fever and general malaise. This syndrome, which can occur as a result of a variety of insect sting allergies, including mosquito's bites, was first described by Simons, who observed allergic reactions to mosquito bites masquerading as cellulitis.⁸

Systemic IgE-mediated reactions and anaphylaxis

The presence of cardiovascular (syncope, hypotension and collapse), respiratory (wheeze, stridor and chest tightness) or gastrointestinal symptoms (abdominal cramps and diarrhoea) indicates anaphylaxis. It is useful to note that the inclusion of gastrointestinal symptoms in the definition of anaphylaxis differs from that of food allergy-associated anaphylaxis. This is because many gastrointestinal symptoms in food allergy relate to local mucosal reactivity, where gastrointestinal symptoms in association with insect allergy are systemic reactions. Symptoms of anaphylaxis may precede urticaria or angioedema, or may occur without any cutaneous manifestations whatsoever. Cutaneous angioedema or urticaria, at a site distant to the sting/bite, is a sign of a generalised systemic reaction (mild), but not of anaphylaxis.

When obtaining a history of past reactions, it is important to identify the time between the sting and the development of symptoms, as anaphylaxis usually occurs within 1 h of the sting. A history of mastocytosis, angiotensin-converting enzyme inhibitor and/or beta-blocker use is also important to obtain, as these cofactors may worsen anaphylaxis and complicate response to treatment, although generally more relevant to adult than paediatric practice.

In general, sting anaphylaxis to the vespids (yellow jackets, hornets, common paper wasps) is generally not as severe as the honeybee; however, deaths from paper wasp stings in Australia have been reported.⁹

Investigations

For suspected systemic IgE-mediated reactions

Intradermal skin prick (IDT) and serum-specific anti-venom IgE are the most common investigations performed where bee or wasp systemic allergic reactions or anaphylaxis is considered likely on history. Stinging insects are related to each other in a complex taxonomy (Fig. 2), which in part explains cross-reactive allergenicity.¹⁰ As Australia has many indigenous paper wasps, skin testing with commercial extracts and commercial *in vitro* testing may result in false negatives due to differing allergens. There are no commercial allergen extracts for ant or tick venom currently available in Australia or New Zealand. A

serum-specific anti-JJA venom IgE is currently available in South Australia. With the exception of clinical research studies, there are no other available confirmatory investigations for individuals with a history of allergic reactions to ants, ticks or spider bites/stings.

Serum-specific anti-venom IgE to honeybee, yellow jacket and a limited number of paper wasps is readily available through most laboratories in Australia. Although not generally as sensitive as IDT, these measurements are useful in individuals with severe skin conditions (e.g. eczema) or who are taking medications such as antihistamines. Positive titre serum tests may be useful in conjunction with a convincing history. Serum-specific anti-venom IgE are also useful in resolving disparity between a negative IDT and a convincing history of a systemic reaction to a sting. IDT is a specialised test available under the care of an immunologist.

Neither serum-specific anti-venom IgE levels nor IDT size predicts the severity of subsequent reactions. Many individuals with large IDT may only have LLRs, while other individuals with anaphylaxis may have a weakly positive serum-specific anti-venom IgE test.¹¹

IDT and/or serum-specific IgE tests are not recommended or indicated for individuals who have had LLRs in the absence of systemic symptoms. The risk of these individuals progressing to systemic reaction or anaphylaxis on subsequent sting/s is only slightly higher than that of the general population (approximately 5%³).

Identification of underlying mastocytosis using baseline serum tryptase should be performed in all individuals with a history of anaphylaxis to insect venom and who are undertaking VIT.

Sting Characteristics and Removal

Hymenoptera (bee, wasp and ant)

Only female bees can sting. Approximately 50–140 mcg of venom is delivered in a single bee sting, compared with up to 3 mcg in a vespa wasp sting. The amount of venom injected by the wide range of native paper wasps in Australia is unknown. Bees usually lose their stinger and the attached venom sac in the process of stinging. The stinger can continue to deliver venom for up to 1 min, but the bee cannot re-sting. Wasp and ants do not have barbs on their stingers and can sting multiple times. In general, therefore, the presence of a stinger *in situ* indicates a bee sting. Stingers should be flicked off, as attempting to pull off the stinger may result in injection of more venom via its attached sac.

The Australian native bull and jack jumper ants (genus *Myrmecia*) are aggressive and capable of stinging multiple times when provoked. This typically results in pain, swelling and burning along with LLRs. Seventy per cent of those with allergic reactions to their first ant sting will experience a second allergic reaction if re-exposed. JJA venom is estimated to be four times more potent than bee venom and has caused at least four recorded deaths in Australia.¹²

Ticks

Allergy to tick bites usually manifests as LLRs associated with pain, swelling and itching. Itch, one of the cardinal symptoms of

tick allergy, can typically last for days. Anaphylaxis has been reported.^{13–15} Tick allergy has been associated with the subsequent development of red meat allergy, in some atopic adults. This can occur 1–6 months after being bitten. Allergy to beef is most common, followed by lamb, pork and game, and is likely related to the cross-reactive allergen galactose- α -1,3-galactose beta-gal.¹⁶

Ticks should not be forcibly removed. Use of chemicals such as turpentine should be avoided as they can cause an increase in allergen inoculation, and thus, provoke a more severe allergic reaction. Experienced physical removal (e.g. using tick forceps) is effective. Use of Aerostart (a lubricant used in automotive industry; CRC Industries Pty Limited, Sydney, NSW, Australia) is also recommended; however, as the lubricant is highly flammable, extreme caution in its supervised use is recommended. The ether in Aerostart freeze-dries and instantly kills the tick, resulting in the tick falling off before injecting the allergen. Unfortunately, there is no effective test or allergen extract currently available for immunotherapy for tick allergy. A fact sheet is available from the ASCIA website (<http://www.allergy.org>).

Treatment of Insect Allergy

Preventative measures

For tick allergy, long-sleeved shirts and trousers should be worn with trouser legs tucked into long socks. Conical hats are recommended. Clothes should be brushed to remove ticks before coming indoors and children should be checked daily for ticks. Caution should be exercised in areas where bees and wasps gather (e.g. parties). Shoes (not thongs) should be worn to prevent feet from being bitten. Topical insect repellents containing N,N-diethyl-meta-toluamide can be helpful (<15% suitable for children).

Local reactions

LLRs are usually adequately treated with antihistamines and cold compresses. Oral corticosteroids have also been used in severe cases of Skeeter syndrome. VIT has been used very rarely to reduce morbidity³ in extreme circumstances but is not generally recommended for this type of reaction.

Systemic allergic reactions and anaphylaxis

All children with a history of a generalised systemic allergic reaction to an insect should be provided with an anaphylaxis action plan (ASCIA)¹⁷ and in most circumstances, an adrenaline autoinjector, irrespective of whether they are also receiving VIT. In children with a history of only mild systemic reactions (urticaria and/or angioedema), other risk factors such as asthma, distance from medical facilities and risk of re-exposure should be considered prior to a decision not to provide an adrenaline autoinjector. In the advent of anaphylaxis, early administration of intramuscular adrenaline in anaphylaxis is imperative and reduces the risk of morbidity and fatalities.¹⁸ It is also essential to lay the patient flat and provide oxygen and intravenous fluids as required and outlined in the current Australian

Prescriber Wall Chart. Unlike food anaphylaxis, adrenaline is indicated for vomiting and abdominal pain arising from insect anaphylaxis. Individuals with a history of systemic reactions (including anaphylaxis) to insect sting require a prescription of an adrenaline autoinjector (300 mcg adrenaline if >20 kg, 150 mcg if between 10 and 20 kg, 500 mcg for >60 kg) and advice on the autoinjectors' appropriate use. Two brands of autoinjectors with different mechanism of delivery, the EpiPen (Alphapharm, Sydney, NSW, Australia) and the Anapen (Lincoln Medical, Salisbury, UK), are currently available in Australia. Anaphylaxis action plans are available from the ASCIA website (<http://www.allergy.org>).

Medical alert bracelets are recommended for individuals at risk of anaphylaxis. Non-sedating antihistamines may be used for symptomatic relief in mild systematic allergic reactions and local reactions. They should never be used in preference to adrenaline in the presence of symptoms of anaphylaxis. Oral corticosteroids have little role in the treatment of IgE-mediated systemic allergic reactions. They may be useful in LLR, where swelling causes significant ongoing pain.

Specific immunotherapy

VIT is commercially available in Australia for honeybee, paper wasp and yellow jacket. VIT is very effective.¹⁹ Most will experience mild local reactions if stung during the course of VIT. Honeybee VIT is generally less effective than vespid VIT, providing shorter duration of protection following cessation of treatment and more chance of systemic reactions with re-stings.²⁰ Studies indicate that the risk of a recurrent systemic reaction is approximately 5% or lower after completing a course of VIT.^{21,22}

All children who suffer from a systemic reaction to insect venom should be referred to an immunologist for evaluation and testing. VIT is offered where there is a history of anaphylaxis and a positive test. VIT is not usually indicated in isolated cutaneous systemic reactions (generalised urticaria and angioedema), as these children have a low risk of anaphylaxis on re-exposure compared with adults, where progression to anaphylaxis has been reported.⁴ VIT should however be considered in children with isolated systemic skin symptoms if they live in a remote location or if psychological distress prevents them from having a normal outdoor life or where there is a higher risk of insect stings, such as having parents who are bee-keepers.

VIT carries a risk of anaphylaxis and hence should only be performed by an experienced physician with ready access to resuscitation equipment, preferably initially in a hospital setting. There are various regimens for VIT, all of which include a build-up phase with progressive increase in the dosage of venom injected subcutaneously until a maintenance dose is reached. The regimens differ in the time required to reach this maintenance dose. The common 'modified rush' regimen reaches the maintenance dose in 2–3 weeks compared with 4–6 months in the traditional regimen. There is conflicting evidence regarding whether the modified rush regime is associated with increased adverse events;^{23–26} however, it is widely used in clinical practice in Australian settings.

VIT – side effects

A significant proportion of patients undergoing VIT is reported to experience adverse reactions. This varies from mild injection site reactions to anaphylaxis. A recent Cochrane review reports an average systemic reaction rate of 2.8% for wasp VIT compared with 14.2% for bee VIT.¹⁹ LLRs are common (occurring in 50% of patients) but are not associated with an increased risk of anaphylaxis. Pre-medication with an oral antihistamine does not interfere with VIT efficacy and is effective in minimising side effects. Omalizumab (an anti-IgE) has been used in some individuals who have experienced recurrent anaphylaxis during VIT.²⁷

VIT – duration of therapy

It was previously generally accepted that specific immunotherapy would confer lifelong immunity. However, recent studies have indicated that after 3–5 years, the chance of a reaction is approximately 10%. These subsequent reactions are usually mild and usually less severe than pretreatment reactions.^{23–25} Indefinite therapy is considered in individuals who have experienced a life-threatening reaction to honeybee stings and in those with mastocytosis.¹³ Patients who have significant cardiovascular or respiratory disease may also benefit from indefinite therapy. Consideration should be given for the ongoing provision of an adrenaline autoinjector post-VIT.

VIT – mechanism of action

The mechanism of VIT is not completely understood but is believed to involve both humoral and cellular mechanisms. Successful VIT is associated with production of venom-specific IgG4, which is postulated to function as a 'blocking antibody' interfering with IgE cross linkage.²⁸ Changes in T cell cytokine profiles, with a shift away from T helper cell type 2 (Th2) (interleukin 4,5) responses to Th1(interferon- γ) and enhanced T-regulatory responses (interleukin 10 and IgG4)²⁹ have been observed. Osteopontin – biomarker for the Th1 response – has been studied with gene array analysis as a possible means of assessing the Th2–Th1 shift in VIT.³⁰

The reduction of venom-specific IgE usually accompanies successful VIT.³¹

Summary

Insect allergy is common and can occasionally cause anaphylaxis. LLRs occur commonly in children. The risk of progression to a systemic reaction following a history of large local reaction is very low. Anaphylaxis to insect stings/bites occurs more commonly in adults than in children. History is the most important aspect of diagnosis as both skin- and serum-specific anti-venom IgE testing can be positive in non-allergic individuals. Simple preventative measures such as protective clothing, avoidance of the causative insect and insect repellents are helpful. For individuals with known past anaphylaxis, a medical alert bracelet should be worn and an adrenaline autoinjector should be carried at all times. A referral to a clinical immunologist/allergist is recommended for those who have experienced anaphylaxis.

Multiple Choice Questions

- 1 A 5-year-old child presents with localised swelling to his arm after being stung by an unidentified insect 8 h ago. He has a history of LLRs to stings in the past. On examination, he has a large erythematous swelling on his lower forearm, 10 cm in diameter, hot and mildly tender to touch. There is no current generalised urticaria or angioedema, and his mother does not recall any of these symptoms at the time of the sting. Which of the following is the MOST appropriate management?
 - a. Oral antihistamine
 - b. Oral antihistamine and oral prednisolone
 - c. Intramuscular adrenaline
 - d. Referral for immunotherapy
 - e. Simple analgesia only
- 2 A 7-year-old girl is stung by a bee. In which of the following clinical presentations is immunotherapy indicated?
 - a. Large local reaction
 - b. Generalised urticaria
 - c. Widespread angioedema
 - d. Coughing, vomiting and feeling faint immediately after the sting
 - e. Generalised urticaria and angioedema in a child with asthma
- 3 A 5-year-old boy is brought to the emergency department by his mother after she discovered a tick on his neck. He has a past history of LLRs to tick bites. What is the appropriate removal method in this situation?
 - a. Use a pair of tick tweezers and manually remove
 - b. Leave it alone, it will eventually drop off on its own
 - c. Spray with insecticide
 - d. Douse with alcohol
 - e. Spray with Aerostat, without manual removal

Answers

Question 1: a is the correct answer.

This child has large local reaction to stings. Oral antihistamine is the treatment of choice. Often antihistamines may be needed for several days and reaction can last up to a week in duration. Oral prednisolone is not usually indicated, unless the swelling is in a position where swelling will cause a significant discomfort or loss of function. He does not have symptoms consistent with anaphylaxis; thus, IM adrenaline is not warranted. In anaphylaxis, symptoms often occur immediately with the majority of symptoms occurring within 1–2 h of the event and must involve either the respiratory, gastrointestinal or cardiovascular system. Immunotherapy is not indicated for LLR as progression to anaphylaxis on subsequent bites/stings is extremely rare.

Question 2: d is the correct answer.

The indication for immunotherapy in children is sting anaphylaxis. Large local reaction and systemic cutaneous symptoms (urticaria and/or angioedema) are usually not indications for immunotherapy. Respiratory involvement often manifests as a persistent cough, whereas feeling faint or collapse suggests hypotension. Vomiting is considered anaphylaxis in sting allergy as it often precedes hypotension in children and is a manifestation of a serious systemic reaction.

A history of asthma in a child puts them at higher risk of anaphylaxis. The absence of respiratory/cardiovascular/gastrointestinal symptoms following the bee sting would indicate a generalised cutaneous reactions only. The risk of developing anaphylaxis on repeat sting is about 5% in children with generalised cutaneous reactions only, similar to that of the general population; thus, immunotherapy is not indicated. An adrenaline autoinjector is generally warranted in the situation of generalised cutaneous reactions and always indicated where previous insect anaphylaxis has occurred.

Question 3: e is the correct answer.

The safest way to remove a tick is to use Aerostat that freeze-dries the tick, causing it to fall off. Any manual manipulation may result in the tick burrowing deeper and injecting more allergen. Insecticides and alcohol act as irritants to the tick, causing the insect to discharge more allergen. Not removing the tick will increase the chance of a large local reaction and less commonly predispose to possible infections and very rarely, in young and small children, tick paralysis.

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