BSACI GUIDELINES

Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines

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Summary

This guidance for the management of patients with hymenoptera venom allergy has been prepared by the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI). The guideline is based on evidence as well as on expert opinion and is for use by both adult physicians and pediatricians practising allergy. During the development of these guidelines, all BSACI members were included in the consultation process using a web-based system. Their comments and suggestions were carefully considered by the SOCC. Where evidence was lacking, consensus was reached by the experts on the committee. Included in this guideline are epidemiology, risk factors, clinical features, diagnostic tests, natural history of hymenoptera venom allergy and guidance on undertaking venom immunotherapy (VIT). There are also separate sections on children, elevated baseline tryptase and mastocytosis and mechanisms underlying VIT. Finally, we have made recommendations for potential areas of future research.

Executive Summary

1. Patients experiencing a systemic reaction (SR) to wasp or bee stings should be referred to an allergy specialist for investigation and management.
2. In the United Kingdom, wasp venom allergy is more common. Bee venom allergy usually occurs in beekeepers, their household members or where there is occupational risk.
3. Venom allergy is a common cause of anaphylaxis and may be fatal. The main features of SRs are rapid onset generalized urticaria, angio-oedema, bronchospasm/laryngeal oedema and hypotension with collapse and loss of consciousness. Hypotension is the dominant feature and may occur alone.
4. Demonstration of venom-specific IgE is the cornerstone of diagnosis and skin testing (skin prick and intradermal) remains the first line of investigation. All patients should be tested to both venoms. While double-positive intradermal skin tests to both bee and wasp venoms are rare, dual-positive serum-specific IgE is common even in the presence of clinical allergy to a single member of the hymenoptera family.
5. Baseline tryptase should be measured in all patients with SRs, as those with raised levels have a higher risk of severe SRs.
6. Patients with a history of SR should be immediately provided with a written emergency management plan, an adrenaline auto-injector and educated in its use.
7. Venom immunotherapy (VIT) is effective in 95% of patients allergic to wasp venom and about 80% of those allergic to bee venom.
8. VIT is recommended for all patients with a severe SR after a sting and in many patients after a SR of moderate severity.
9. VIT is usually not indicated for less severe sting-induced SRs unless additional risk factors are present for example: a raised baseline tryptase, a high likelihood of future stings, (bee keeping, or occupational exposure), or effect on quality of life (QOL).
10. Children generally have less severe reactions than adults and a better prognosis and therefore VIT should only be considered for the small percentage that have severe sting-induced systemic allergic reactions.

11. VIT must not be undertaken in the absence of demonstrable venom-specific IgE. In patients with a recent history of anaphylaxis or SR, where venom-specific IgE is not demonstrable, allergy testing should be repeated.

12. VIT should be carried out only by allergy specialists with experience and knowledge in this field and in centres undertaking VIT in significant numbers of patients and where the team has expertise in treating anaphylaxis.

13. In the United Kingdom, the usual duration of VIT is 3 years. Longer or even life-long treatment in patients with a raised baseline tryptase is not advocated in the United Kingdom because this is not evidence-based.

14. Many patients with a raised baseline tryptase and a SR have an indolent form of 'mastocytosis' and are at higher risk of SRs during VIT although VIT remains the treatment of choice.

15. An adrenaline autoinjector should be provided during up-dosing of VIT and British Society for Allergy and Clinical Immunology (BSACI) also recommends its long-term prescription for the following:
    a. If during VIT the patient continued to experience allergic reactions
    b. After VIT, those at continuing risk of multiple stings, e.g. those with an occupational risk or a beekeeper
    c. After VIT, patients with an elevated baseline tryptase or mastocytosis.

16. Patients should be advised on ways of minimizing their risk of further stings.

Introduction

This guidance is intended for use by specialists involved in the investigation and management of patients with hymenoptera venom allergy. This updates the previous BSACI position paper [1]. It is recommended that all patients experiencing a SR in response to insect stings be referred to an allergy specialist for further investigation.

Evidence for these recommendations was collected by electronic literature search using the key words – hymenoptera, venom, allergy, VIT in combination with skin test, anaphylaxis, mastocytosis, bee keeper, rush, ultra-rush, protocols, antihistamine, epidemiology, cross reactivity, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, basophil activation test (BAT) and CD63. Each article was assessed for its suitability.

Epidemiology

Questionnaire-based studies have shown that 56–94% [2] of the population are stung by an insect of the hymenoptera family at least once in their lifetime. While the prevalence of sensitization varies between 9.3% and 38.7% [3] in the adult population, large local reactions (LLR) occur in 2.4–26.4% [3–6] and SRs in 0.3–7.5% [5–10]. The differences between studies have been attributed at least in part to confounding variables including geographical location, data collection technique, definition of anaphylaxis and degree of exposure. In bee keepers and their family members, the sensitization rate to bee venom is 30–60% [11], the prevalence of local reactions is 9–31%, and the prevalence of SRs is 14–32%. Venom allergy is an important cause of anaphylaxis accounting for about one quarter of cases where the cause was determined in adults [12]. Fatalities following insect stings are rare and occur in 0.03–0.48 per 100 000 inhabitants per year [2, 3, 11]. These data are largely from studies carried out in the United States and Europe. There are no published data on prevalence of hymenoptera venom allergy from the United Kingdom. However, Pumphrey [12, 13] reported that between 1992 and 2001 in the United Kingdom, 47 out of 214 deaths, due to anaphylaxis, were caused by bee or wasp stings and the average age of death was 50 years [13].

Risk factors

The frequency of a systemic reaction is affected by the following factors

i. *Preceding reaction*: The risk for SRs in the normal population is increased by 58% if preceded by a sting within 2 months even if the first sting was well tolerated [14]. The estimated risk of a SR is 5–15% [7] after a previous LLR and 40–60% [15] after a SR.

ii. *Sensitization to venom*: IgE sensitization to venom is a risk factor for subsequent SRs [16]. However the level of venom-specific IgE does not correlate with the severity of the SR and some patients with barely detectable venom-IgE can have near-fatal anaphylaxis [17, 18] In addition, positive skin tests and venom-specific IgE are also found in patients without a history of reactions or with only local reactions and therefore these tests cannot be used as a screening tool for severe venom allergy.

iii. *Venom*: The risk for a SR is greater in a bee venom sensitized patient compared with those sensitized to wasp venom [11].

iv. *Bee keepers*: Bee keepers are frequently stung and most bee venom allergy occurs in bee keepers and their household members. SRs are more common in the early years of bee keeping and those who have < 15–25 stings per year are at higher risk for SRs after bee stings compared with bee keepers receiving > 200 stings who appear to be protected [11].

v. *Atopy*: Venom allergy does not appear to be more common in atopic individuals [9].

The severity of a systemic reaction is affected by the following factors

i.   *Age*: The majority of SRs in the pediatric age group are cutaneous but in adults cardio-respiratory compromise is common [2, 19]. Near-fatal or fatal outcomes are extremely rare in children and more likely to occur in those with elevated baseline serum tryptase or mastocytosis and co-existing cardiac and respiratory disease [2, 20].

ii. *Cardiac and respiratory disorders*: Diseases compromising cardiac or respiratory reserve may increase the severity of SRs [20]. Concurrent treatment with β-blockers could adversely affect the response to adrenaline, and a recent study has shown that treatment with ACE inhibitors is a risk factor for SRs [21, 22].

iii. *Baseline tryptase and mastocytosis*: Tryptase is a specific marker for mast cell and basophil degranulation in type-1 hypersensitivity reactions. Studies in the last decade have shown that up to 25% of patients experiencing severe anaphylaxis (i.e. with loss of consciousness and/or cardiac arrest) have an elevated baseline tryptase [23, 24] with or without systemic mastocytosis. Interestingly, most of these patients do not suffer from symptoms of mastocytosis as it is the anaphylaxis to insect stings that prompts investigation [25]. There are reports of fatalities [26] from insect stings in such patients as well as a higher rate of adverse reactions to VIT [25].

Entomology of hymenoptera

Insects of the order hymenoptera include bees, wasps and ants. Stings from these insects can cause fatal anaphylaxis. Knowledge of this classification is helpful in the management of hymenoptera venom allergy, particularly with diagnostic testing and choosing the correct venom for immunotherapy in patients who have experienced life-threatening allergic reactions. The insects of hymenoptera relevant to UK clinical practice (Fig. 1) are wasp (*Vespula vulgaris*) and honey bee (*Apis mellifera*). Hornets (*Vespa crabo*) are also found in Britain, but are relatively uncommon and largely confined to southern parts of the country. The description and habitat of these insects is summarized in Table 1. The scientific and common nomenclature of Hymenoptera insects worldwide are listed in Table 2 [27].

Venom allergens

Hymenoptera venom contains several low molecular weight components, but most are glycoproteins (10–50 kDa). Vespids usually do not lose their sting after stinging and hence are capable of stinging the victim several times. In contrast, bees typically lose their barbed sting. While bees release a large amount of venom per sting (50–140 μg), the amount of venom in a vespid sting is relatively less (2–17 μg). The venoms of relevance to UK clinical practice are summarized in Table 3.
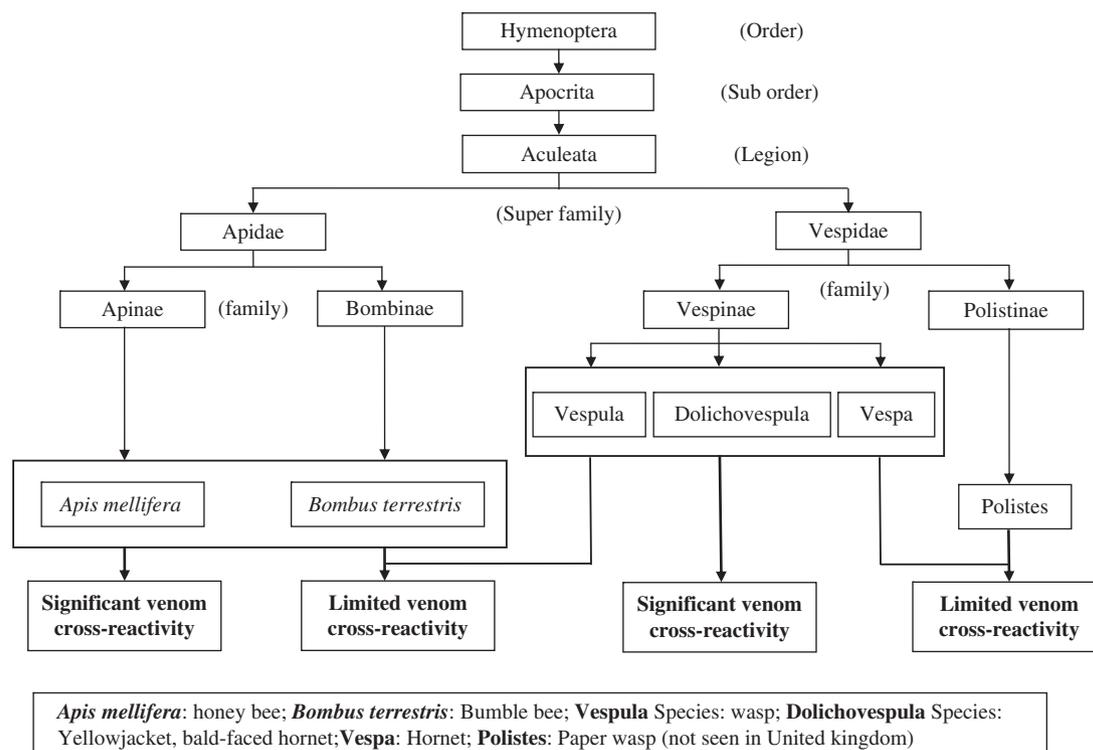

Apis mellifera: honey bee; **Bombus terrestris**: Bumble bee; **Vespula** Species: wasp; **Dolichovespula** Species: Yellowjacket, bald-faced hornet; **Vespa**: Hornet; **Polistes**: Paper wasp (not seen in United kingdom)

Fig. 1. Classification of hymenoptera insects relevant to UK practice.

Table 1. Description and habitat of stinging insects in the United Kingdom

Insect	Description	Image*	Field stings–usual time of year
Wasp (*Vespula vulgaris*)	~19 mm long, yellow head with black stripes, black thorax with yellow sides, yellow abdomen with black bands, black antennae and yellow legs.		March–October
European Hornet (*Vespa crabo*)	35 mm long, reddish brown head, black and brown shaded thorax, yellow and black shaded abdomen.		March–October
Honey bee (*Apis mellifera*)	12.7–25.3 mm, covered with short dense hair, usually golden brown and black, abdomen striped.		March–October, occasionally even in warm winter days
Bumble Bee (*Bombus pascuorum, Bombus lapidarius, Bombus pratorum, Bombus terrestris, Bombus lucorum, Bombus hortorum*)	19.1–38 mm head to tail, black and yellow soft body hairs and appear fuzzy, often in bands, some have orange or red in their bodies, or entirely black.		February–October

*Black bar below the image indicates relative size of the hymenoptera species, the dashed line indicates variation within the species (images obtained with permission from http://www.naturalvisions.co.uk (wasp image) and from http://www.naturephoto-cz.eu (bee, bumble bee and hornet images).

There is substantial IgE and clinical cross-reactivity between *wasps* and *hornets* (subfamily vespinae) [28–30]. There is only limited [31] specific IgE cross-reactivity between wasp and bee venoms due to the hyaluronidase component but this is rarely clinically relevant [32–35]. Paper wasps are not currently found in the United Kingdom but occur in other parts of Europe. There is limited IgE cross-reactivity between wasp/hornet and paper wasp venom [31]. Venoms from bumble bee and honey bee are highly cross-reactive clinically which is consistent with the degree of structural homology found in the enzymes [36, 37]. About 75% of sera from patients allergic to honey bee venom react to *in vitro* tests with bumble bee venom, and 85% of sera from patients with a history of allergy to bumble bee stings demonstrate positive tests to honey bee venom [37]. However, bumble bee venom contains several

Table 2. Scientific and common names of hymenoptera worldwide (reproduced and adapted with permission from Fernandez [27])

Scientific	UK	USA	Danish	Dutch	French	German	Italian	Spanish
Apis Mellifera	Honey bee	Honey bee	Honningbi	Bij	Abeille	Biene	Ape	Abeja
Bombus	Bumble bee	Bumble bee	Havehumle/Humlebi	Hommel	Vrai Bourdon	Hummel	Bombo	Abejorro
Vespula	Wasp	Yellow Jacket	Hveps/Gedehams	Wesp	Guêpe	Wespe	Vespa (Giallone)	Avispa
Dolicho-vespula	Wasp	Hornet or aerial Yellow Jacket	Hveps/Gedehams	Wesp	Faux Frelons	Wespe	Calabrone americano	Avispa
Vespa	Hornet	European Hornet	Stor gedehams	Horzel	Vrais Frelons	Hornisse	Calabrone Europeo	Avispón
Polistes	*	Paper Wasp	Paper hveps	Veldwesp*	Guêpe poliste	Feld-Wespe	Polistes	Avispa Papelera

*Not found in the United Kingdom and the Netherlands.

Table 3. Hymenoptera Venom Allergens relevant to UK practice

Venom	Component (in bold are major allergens)
Honey bee (*Apis mellifera*)	Phospholipase A2 (PLA2)
	Hyaluronidase
	Acid Phosphatase
	Mellitin
	Allergen C (dipeptidylpeptidase)
	Serine Protease
	10 kDa protein
Bumble bee (*Bombus* spp.)	Phospholipase A2
	Hyaluronidase
	Acid Phosphatase
	Protease (of tryptic amidase specificity)
	Fraction-4
Wasp (*Vespula* spp. and *Dolichovespula* spp.)*	Antigen 5
	Phospholipase A1
	Hyaluronidase
Hornet (*Vespa* spp.)	Antigen 5
	Phospholipase A1
	Hyaluronidase

*Called yellow jacket in the United States. Wasp species encountered in United Kingdom is *Vespula vulgaris*.

minor allergens that are not found in honey bees [37] (Table 3).

Thirty percent of patients with a clinical history of hymenoptera venom allergy are positive to both bee and wasp allergens on *in vitro* testing for serum-specific IgE but clinical double-reactivity to apidae and vespidae is rare [9, 38]. Double positivity seen in diagnostic tests, particularly with *in vitro* methods, is due to 50% sequence identity of hyaluronidases and cross-reactive carbohydrate allergenic determinants between venoms (hyaluronidases, acid phosphatase and phospholipase A2) and plants (e.g. pollens). The double positivity seen with *in vitro* methods can often be discriminated by skin tests [38] where positive results are more likely to be seen only to the venom to which the individual is truly sensitized.

Intradermal skin tests rarely show double positives (33). Another approach is to use RAST inhibition tests with venoms and cross-reactive carbohydrate determinants [35, 39, 40], but in the United Kingdom this remains a research tool. A recent report has highlighted the utility of estimation of IgE to species-specific recombinant major allergens including Api m1 (bee venom) and Ves v5 (vespula) for identifying true sensitization when dual positivity is present [41]. Results from all diagnostic tests must be interpreted in the context of the clinical history in order to choose the appropriate venom for immunotherapy.

Allergic reactions to hymenoptera venom

Minor local reactions to insect stings are normal and do not warrant allergy testing. However, some local reactions can be large and troublesome and are characterized by oedema, erythema or pruritis. An area of induration with a diameter of > 10 cm and which peaks between 24 and 48 h and then subsides is referred to as a LLR [42]. The literature relating to LLR is poor and fragmentary. It is estimated that the risk of developing a SR after a LLR is relatively low (5–15%) and this observation is consistent in adults and children [16, 19, 43]. Another study has suggested that a LLR does not significantly increase the risk of a SR to future stings [8].

SRs are usually of rapid onset within minutes of the sting. They vary in severity, from minor urticaria through to loss of consciousness (Table 5). Hypotension is the key severe feature, but there is also a high incidence of respiratory and cutaneous involvement. Patients with severe SRs often suffer a feeling of impending doom. In some patients, there is sudden hypotension, (collapse and loss of consciousness) with no other features. Conjunctivitis may occur but is often not noticed; rhinitis is uncommon. Rare manifestations are seizures and incontinence. Less commonly patients develop a biphasic anaphylactic response. Fatal reactions are rare but almost certainly under-recognized. Where data was ascertained, insect stings

Table 4. Natural history of venom allergy

Nature of index reaction	Incidence of systemic reaction to subsequent sting [numbers of patients (or stings where specified)]	Nature of subsequent sting	Author
Mild/ Moderate systemic	4/13 (31%) (bee)	Challenge sting	Blaauw and Smithuis [144]
	2/7 (29%) (wasp)	Challenge sting	Blaauw and Smithuis [144]
	2/14 (14%) (of stings; wasp/bee)	Challenge sting	Engel et al. [146]
	15/42 (36%) (wasp)	Challenge sting	Kampelmacher and van der Zwan [147]
	4/9 (44%) (bee)	Challenge sting	Kampelmacher and van der Zwan [147]
	4/9 (44%) (wasp/bee/hornet)	Challenge sting	Parker et al. [148]
	0/11 (0%) (of stings)	Field sting	Savliwala and Reisman [149]
	6/18 (33%) (of patients; wasp/bee)	Field sting	Reisman et al. [47]
	8/74 (11%) (wasp/yellow jacket/ hornet/bee)	Field sting	Schuberth et al. [150]
Severe systemic	15/25 (60%) (bee)	Challenge sting	Blaauw and Smithuis [144]
	10/17 (59%) (wasp)	Challenge sting	Blaauw and Smithuis [144]
	3/33 (9%) (wasp)	Challenge sting	Kampelmacher and van der Zwan [147]
	3/7 (43%) (bee)	Challenge sting	Kampelmacher and van der Zwan [147]
	3/7 (43%) (wasp/bee/hornet)	Challenge sting	Parker et al. [148]
	3/14 (21%) (of stings; wasp/bee)	Field sting	Savliwala and Reisman [149]
	11/41 (27%) (wasp/bee)	Field sting	Lantner and Reisman [151]
	8/10 (80%) (of patients; wasp/bee)	Field sting	Reisman et al. [47]
Systemic (severity not reported)	7/12 (58%) (wasp/bee)	Challenge sting	Hunt et al. [44]
	72/119 (61%) (wasp/yellow jacket/ hornet/bee)	Field sting	Settipane et al. [46]

Response to subsequent stings in patients who have previously sustained a systemic reaction.

Table 5. Classification of systemic allergic reactions to bee or wasp stings

Type	Severity	Features
Systemic	Mild	Pruritus, urticaria, erythema, mild angio-oedema, rhinitis, conjunctivitis
	Moderate	Mild asthma, moderate angio-oedema, abdominal pain, vomiting, diarrhoea, minor and transient hypotensive symptoms (light headedness, dizziness)
	Severe	Respiratory difficulty (asthma/laryngeal oedema), hypotension, collapse or loss of consciousness, Rare: double incontinence, seizures, loss of colour vision

accounted for one quarter of all anaphylactic deaths in the United Kingdom each year [12]. In fatal cases, the average time from sting to death was 10–15 min [13].

Natural history

A substantial proportion of patients (20–100% in different studies) with a history of a generalized reaction to a sting have no such reaction to a subsequent sting; that is, spontaneous improvement is common (Table 4). This was evident from the original double-blind placebo-controlled trial of pure VIT, where after 6–10 weeks treatment, only 58% of the group on placebo injections had a SR to sting

challenge, i.e. 42% had no reaction to sting [44]. This effect has been demonstrated in response to both field stings and sting challenge in untreated patients. A SR was less likely after a mild–moderate SR than if the initial reaction had been severe. Children do particularly well; one study showed that 81% with a history of mild generalized reactions did not react to a subsequent sting and no reaction was more severe than the preceding one [45].

In routine clinical practice, it may be difficult to quantify the risk of anaphylaxis in a patient with a history of mild–moderate SR. In one study, the severity of a SR to a subsequent sting was reduced in 45% of patients, similar in 43% and in only 12% more severe [46]. However, the course can also be variable: a series of stings may result in a generalized reaction, no reaction, and then another generalized reaction. When the initial SR is mild (cutaneous features only) the prognosis in adults is good: in one study 98% of patients had either a similar or no reaction to the subsequent sting [47]. A more recent study has shown that a less severe SR to hymenoptera insect sting is a risk factor for anaphylaxis to future stings although the proportion with preceding mild (cutaneous-only) SRs was not specified [22]. A problem with interpreting older studies is that other risk factors such as raised baseline tryptase, which would influence outcome, were not recognized. Reasons for the variable outcome are not well understood but may include the interval from the last sting (the longer the interval the lower the risk of

another generalized reaction), the patient's immune response at the time of the sting (this will change over time), the dose of venom injected, and the site of the sting.

Clinical features

When taking a medical history it is helpful to classify the severity of each sting as local or systemic and any SR as mild, moderate or severe as this influences management. Table 5 shows a classification of systemic allergic reactions to stings.

Venom allergy in children

Hymenoptera stings in children occur usually during outdoor play. Children with venom allergy are usually non-atopic and those with food allergy are not at increased risk [48]. LLR are common in children and no further investigation is necessary.

The prevalence of SRs to hymenoptera stings in the pediatric population is unknown [48]. Most children with systemic allergic reactions to insect stings have skin manifestations only. A small percentage of children will have more severe sting-induced systemic allergic reactions but fatal reactions are rare [12, 49, 50]. The severity of the initial reaction is of prognostic value. In children with a history of a mild SR, there was no SR to 91% of subsequent stings. 32% of children who have moderate–severe SRs to insect stings have reactions of similar severity following re-stings [51]. When subsequent SRs have occurred in children almost all were less severe and none more severe [43]. The risk of systemic allergic reactions to subsequent stings declines slowly with time although the risk of a SR can persist in up to 20% on long-term follow-up [51, 52].

Non–allergic manifestations

Rare toxic reactions can occur with multiple simultaneous stings manifesting as delayed haemolysis, nephropathy, coagulopathy and neurological symptoms. There are isolated case reports of unusual reactions attributed to hymenoptera insect stings [53–61]. There is no evidence that these are IgE-mediated although the underlying mechanisms are not known. A multi-disciplinary approach with input from other specialists may be required and treatment is usually conservative. Reports of unusual reactions to hymenoptera insect stings are summarized in Table 6. Immunotherapy is not indicated and should not be attempted.

Factors influencing the risk of a future reaction

Sensitization *per se* and levels of venom-specific IgE do not predict the likelihood and severity of a future reaction [2]. As with field stings, the negative predictive value of a

Table 6. Unusual non-allergic manifestations attributed to hymenoptera insect stings [53–61]

Type	Manifestations
CNS	Acute disseminated encephalopathy
	Guillain Barré Syndrome
	Myasthenia Gravis
	Peripheral Neuritis
Haematological	Thrombocytopenia Purpura
	Henoch–Schonlein Purpura
	Haemolysis
	Coagulation defects
Muscle	Rhabdomyolysis with acute renal failure
Renal	Acute Renal Failure due to interstitial nephritis/tubular damage
	Nephrotic syndrome
Respiratory	Alveolar Haemorrhage
Eye	Direct sting causing corneal damage and cataract
Toxic (from multiple stings usually > 50)	Renal failure, rhabdomyolysis, cerebral oedema, haemolysis, clotting disorders, sting site necrosis.

CNS, central nervous system.

sting challenge in assessing clinical reactivity is poor and therefore not recommended in routine clinical practice [62]. An elevated baseline tryptase increases the risk and severity of a SR. Clinical factors must also be considered for example the patient's occupation influencing the likelihood of further stings, the interval from the last sting and the severity of the initial SR.

Investigations for hymenoptera venom allergy

All patients with a history of SRs should be referred to an allergy specialist for further investigation. A detailed history is key to accurate diagnosis. A clear account of the symptoms and progression of the allergic reaction following the sting should be obtained. Details of the timing of previous stings and subsequent allergic reactions are important. Clues to enable identification of the culprit insect should be sought, e.g. if there was a known wasp's nest or whether the insect left the stinger behind (bees usually leave a barbed stinger behind). The treatment provided including scrutiny of emergency room records may aid the decision on whether to offer immunotherapy.

Demonstration of venom-specific immunoglobulin E

i. *Skin testing*: Skin testing is the gold standard investigation for hymenoptera venom allergy because a result is immediately available during the initial consultation and provides greater discrimination between bee and wasp sensitization than serum-specific IgE to whole venom. Skin tests are also more often positive than serum-specific IgE and correlate better with history.

Serology alone may thus result in under-diagnosis or incorrect identification of the insect [38]. Skin prick testing (SPT) should be undertaken with standardized venom extracts (1–100 µg/mL) [3] with both bee and wasp venoms and positive (histamine) and negative controls. A weal diameter of at least 3 mm greater than the negative control indicates the presence of specific IgE. If SPT are negative in patients with a strong clinical history, intradermal testing (IDT) is recommended using concentrations of between 0.001 and 1 µg/mL venom [3, 4, 63, 64]. A volume of 0.03 mL of the extract is injected intradermally to raise a bleb of diameter 3–5 mm and an increase in weal diameter of 3 mm at 20 min is considered positive [65]. A lower starting concentration for IDT can be considered in patients with a history of severe anaphylaxis. SRs have been reported during skin testing, hence these investigations should be carried out only by experienced personnel and in a clinic where treatment for anaphylaxis is readily available.

ii. *Serum-specific IgE*: This should be undertaken in a clinical pathology accredited laboratory. Serum-specific IgE is estimated by standardized solid phase enzyme immunoassay and a level of $\geqslant 0.35$ kU/L considered positive. Skin test reactivity and levels of serum-specific IgE do not correlate with clinical reactivity and hence the result must be interpreted in conjunction with clinical history. Serum-specific IgE should be used as an adjunct to skin testing, particularly when the latter are negative or indeterminate. Double positivity to wasp and bee venom occurs in about 30% of patients, where the patient is clinically allergic to only one insect [38] and is often due to cross-reactivity of venom-specific IgE with certain carbohydrate ligands [40]. Skin testing, particularly intradermal skin testing usually clarifies the situation; intradermal double positivity is uncommon [38].

iii. *Baseline tryptase*: A significant proportion of patients presenting with anaphylaxis to hymenoptera sting have an elevated (> 11.4 µg/L) baseline tryptase [23, 24]. Such patients fall into the 'mastocytosis' spectrum and further investigations including bone marrow examination to exclude systemic mastocytosis or monoclonal mast cell activation syndrome [23, 24, 66, 67] may be necessary. The majority of these patients do not have any evidence of systemic mastocytosis or urticaria pigmentosa. It has been reported that patients with elevated baseline tryptase with or without systemic mastocytosis develop significantly more severe, mostly cardiovascular anaphylactic sting reactions as opposed to those with normal baseline tryptase [68]. Interestingly, the latter group experience urticaria and angio-oedema more often than patients with elevated baseline tryptase who often present with flushing as a dominant cutaneous

Table 7. Investigations in Hymenoptera venom allergy (References see Table 8)

Aimed result	Test details
Demonstration of specific	Skin prick test (10–100 µg/mL) standardized venom extract
IgE to bee and wasp venom	Intradermal test (0.001–1 µg/mL) standardized bee and wasp venom extract
	Serum specific IgE standardized enzyme immunoassay
Serum total IgE	
Baseline serum tryptase	If baseline tryptase is elevated consider follow-up investigations for systemic mastocytosis
Others	Consider follow up investigations for systemic mastocytosis including bone marrow studies for histology, immunophenotyping and c kit mutations.

symptom [68]. Baseline tryptase should be checked in all patients with a history of SRs [23–25, 66, 68, 69].

iv. *Serum total IgE*: This is generally regarded as a non-specific marker but there is limited evidence [70] that a total serum IgE of > 250 kU/L is more likely to indicate asymptomatic sensitization and such patients may be protected from severe anaphylactic shock and loss of consciousness, i.e. only mild–moderate SRs occur. However, this interesting observation requires confirmation in a larger patient population. A summary of investigations for hymenoptera venom allergy is shown in Table 7.

v. *BAT*: This is currently a research tool and is not routinely available in UK National Health Service laboratories. Basophil activation is analysed in whole blood by flow cytometry following incubation with appropriate standardized allergens. Surface expression of CD63/203c is used as a surrogate for basophil activation. BAT correlates well with serum-specific IgE and has comparable sensitivity and specificity to skin tests and serum-specific IgE [71–74]. One study [75] suggested that BAT could predict adverse reactions during VIT but this finding could not be confirmed [76]. BAT is an expensive investigation requiring specialized equipment and skilled personnel and currently has no role in the routine diagnosis of hymenoptera venom allergy or monitoring or predicting adverse reactions to VIT. Comparison of the performance of skin testing with *in vitro* allergy testing is summarized in Table 8.

Sources of error in diagnosis

The following are the most common reasons for diagnostic error:

1. Insect identification – a common error is for patients to state the insect was a bee, when it was a wasp. This

Table 8. Performance of skin tests (ST), basophil activation test (BAT) and serum-specific IgE (SSIgE) in hymenoptera venom allergy [71–74]

	Sensitivity			Specificity		
		Serum specific			Serum specific	
Study	ST	IgE	BAT	ST	IgE	BAT
Ebo et al. 2007 [71]	81.8%[*]	86.4%	83.8%	Not reported	100%	100%
Sturm et al. 2004 [74]	93%[*],[†]	91.2%	87.7%	Not determined	91.2%	87.7%
Erdmann et al. 2004 [72]	100%[*]	76%	92%	Not reported	85%	80%
Sainte-Laudy et al. 2000 [73]	85%[*]	88%	100%	Not reported		

[*]Intradermal skin test (IDT).
[†]Skin prick test (SPT).

information should not be accepted at face value without further questioning and more detailed history.

2. Double-positive serum-specific IgE (positive to both bee and wasp venoms) when the patient is allergic to one only [38]. This can often be clarified by skin prick or intradermal tests supported by the history. If doubt remains, assay of specific IgE to major venom allergens using the recombinant allergens Api m1 and Ves v5 often identifies the causative insect [41].

3. Difficulty in interpreting skin tests. This is a less common problem but skin test weals to venom may be small and only positive at higher concentrations [77].

4. False negative serum-specific IgE. This is not uncommon.
   a. In one series where there was a negative serum-specific IgE and negative SPT in patients with a clear history of SR, IgE blots revealed positive venom-specific IgE in 75% [78].
   b. In patients with SRs, the serum-specific IgE is negative in about 18% but the IDT is negative in only about 2% (C. Lim, personal communication). A North American series reported negative serum-specific IgE and skin tests in 18% of patients with a previous history of SR but on sting challenge only two of 14 (14%) developed a SR. This compared with positive sting challenges in 30 of 141 (21%) subjects with evidence of specific IgE [79].

Management

1. Minimize exposure to further stings (see Appendix A).
2. Provision of management plan for self-treatment of acute allergic reactions: Patients with a history of SR and those with elevated baseline tryptase or mastocytosis and where appropriate their carers (or guardians/parents) should be trained to self-manage allergic reactions. This should include provision of a written treatment plan with appropriate instructions on the use of antihistamine and self-injectable adrenaline and to adopt a supine posture with legs raised should they develop symptoms of hypotension. With children, appropriate liaison with the school is recommended. Patients with previous SRs may also be advised to wear a medical alert bracelet.

3. VIT: This is the only specific treatment that is currently available for patients with a history of SR to a hymenoptera insect sting. Currently in the United Kingdom, licensed standardized allergen extracts (Pharmalgen®, ALK ABELLÓ, Hungerford, UK) are available for honey bee (*A. mellifera*) and wasp (*Vespula spp*). The venom extracts are used for VIT to honey bee and wasp sting allergy respectively. In patients with a history of anaphylaxis to hornets, VIT with Vespula spp. venom should provide effective treatment for both wasp as well as hornet stings due to significant allergenic cross-reactivity (Fig. 1) [80–83]. Epidemiological studies suggest a ~60–70% risk of further SR to a future sting with a reduction of risk after VIT to <5% [44, 84]. VIT is 95–100% and about 80% successful in preventing SRs in wasp and bee sting allergy, respectively [44, 85–89]. Patients with venom-specific IgE and an elevated baseline tryptase or mastocytosis have a dual mechanism for anaphylaxis, and VIT reduces the risk of a systemic allergic reaction and by corollary fatal reactions. Importantly, VIT has been shown to induce a clinically significant improvement in health-related QOL in patients with anaphylactic reactions as well as generalized non-life-threatening responses to yellow jacket stings [90, 91]. This is often an important consideration in selecting patients for immunotherapy.

4. VIT is recommended for all patients with a severe SR after a sting and in many patients after a SR of moderate severity. VIT is usually not indicated for sting-induced cutaneous SRs but may be considered in the presence of additional risk factors for example: raised baseline tryptase, age, likelihood of future stings, (bee keeping, or occupational exposure), remoteness from medical help, effect on QOL, patient preference and co-morbid conditions. VIT is not indicated in patients with a history of only local reactions irrespective of their severity.

Indications for venom immunotherapy in children

VIT should be considered for the small percentage of children who have severe sting-induced systemic allergic reactions. It is likely that they will have similar severe

Box 1. Indications for VIT

Yes	Sometimes*	Not usually*	No
Systemic reaction with hypotension±laryngeal oedema±asthma Must have positive venom specific IgE	Mild asthma, moderate angio-oedema, abdominal pain, vomiting, diarrhoea, mild hypotensive symptoms (light headedness, dizziness) In those at high risk of further stings, e.g. beekeeper/proximity to bees, or occupational exposure, e.g. fruit farmers, gardeners, etc. Other factors, e.g. proximity to medical help, patient preference, effect on quality of life.	Cutaneous systemic reaction, e.g. cutaneous: urticaria+/− mild angio-oedema	Local reaction Toxic reaction Any systemic reaction, independent of severity, if negative specific IgE

*Co-morbid conditions including asthma or other respiratory disease, cardiac conditions, raised baseline plasma tryptase/mastocytosis constitute 'risk factors' and should be carefully considered before making a decision for VIT.

Box 2. Precautions with VIT

VIT is contraindicated in patients with brittle asthma or chronic severe asthma, although may be cautiously initiated in patients with moderately severe asthma after establishing good control.

VIT should not be initiated in patients with psychiatric disorders that will interfere with compliance.

The effects of VIT in patients with disorders of the immune system such as active systemic autoimmunity, immunodeficiency and lymphoid malignancies are not known and therefore the decision to offer treatment should be based on an individual 'risk-benefit' analysis.

VIT should not be initiated in pregnancy but may be continued during pregnancy in patients on maintenance therapy who have tolerated VIT well. However the patient should be informed of the risk of anaphylaxis even during maintenance treatment that could potentially affect the foetus.

In patients on ACE inhibitors and β-blockers (see following sections)

Tricyclic antidepressants should ideally be withdrawn before commencement of VIT and replaced if appropriate by selective serotonin reuptake inhibitors (SSRI) because of potential drug interaction (arrhythmia and hypertension) with adrenaline.

reactions with subsequent stings. Symptoms and signs include: bronchospasm and/or upper-airway oedema and/or hypotension [51]. However, VIT is not indicated for the majority of children who have less severe SRs (urticaria and angio-oedema distant from the sting site) [45] (Box 1 and 2).

Protocols for venom immunotherapy (Appendix B). The time required to reach the maintenance dose varies according to the induction protocol employed. Most UK centres use conventional [92–95] or slow up-dosing regimens (>90% respondents in a national audit [96]). This requires a minimum of 12 weeks with weekly up-dosing. Rush up-dosing [97–99] takes place over 4–7 days and ultrarush [99–101] over 1–2 days. Cluster up-dosing [102–104] comprises a modified rush protocol with several injections at 15–30 min intervals each week reaching maintenance dose in 7 weeks. These protocols have been established with some success and some of the studies are summarized in Table 9.

Some studies have shown comparable safety profiles [98–100, 103–106] for conventional and accelerated protocols. Most studies have shown that the accelerated VIT protocols are associated with a significant increase in the incidence of SRs compared with conventional protocols [97, 101, 102, 107]. This was confirmed in a large multi-centre European study, where rapid dose increase was associated with increased risk of side-effects [107]. These studies have also shown that irrespective of the protocol the SR rate is

significantly higher with bee venom compared with vespid immunotherapy [98, 100, 107]. The significant variation in reported rates of SRs between studies have been attributed at least in part to differences in patient selection criteria for VIT, methods of grading SRs, use of antihistamine pre-medication and dose regimens (in particular cumulative doses in accelerated protocols).

Rush and ultrarush methods are usually reserved for special circumstances and require in-patient management, which almost certainly explains their unpopularity in the United Kingdom. However, given the convenience and relative cost-effectiveness of accelerated protocols, these may be considered in selected lower risk cases.

Irrespective of the protocol employed, once the maintenance dose is achieved, further injections are administered regularly at intervals of 4–8 weeks for the remaining period [108]. The optimum target maintenance dose is 100 μg [108]. However, with treatment failures (i.e. those who develop SRs despite a maintenance dose of 100 μg) an increase in maintenance dose to 150–200 μg should be considered and this approach has been shown to confer protection in some patients only [108, 109]. However, if there are severe SRs to 100 μg, caution should be exercised, the dose reduced and if further SRs occur, VIT discontinued. In patients with a raised baseline serum tryptase, recurrent SRs to VIT may result for two reasons: (i) failure of desensitization, and (ii) mast cell abnormality independent of specific IgE. There is no evidence that the latter would be ameliorated by further VIT.

Table 9. Summary of different VIT protocols and associated systemic reaction

Study	No. of subjects	Protocol	Systemic reactions (SR) %	Venom/s	Comment
Mosbech et al. 2000 [107]	840	Various protocols in 19 European centres combined analysis	20%	HB, vespula	Mild systemic reactions only, inhaled/injected adrenaline used in six subjects, one subject ↓BP; risk factors: females, accelerated protocols and bee venom
Chipps et al, 1980 [93]	44 children	Conventional	6%	HB, YJ	No severe systemic reactions, all systemic reactions to bee venom
Wyss et al. 1993 [95]	35	Conventional	8.6%	HB, YJ	
Lockey et al. 1990 [94]	1410	Conventional	12%	HB, wasp	DBPC study with fexofenadine; helped local reactions and generalized skin reactions including urticaria, pruritis and angio-oedema less in fexofenadine group
Reimers et al. 2000 [101]	57	Ultra-rush	39%	BV	
Birnbaum et al. 1993 [106]	284	46 (rush, 4 days), 21 (ultra-rush-1, 6 h) and 217 (ultra-rush-2, 3 h 40 min)	Rush (28%), ultra-rush-1 (28%) and ultra-rush-2 (6.9%)	YJ, HB	Ultra-rush protocol-2 with lesser cumulative dose was safer
Brehler et al. 2000 [99]	1055	1st: 7–9 days; 2nd : 3–6 days; 3rd: 2 days	1st: 2.2%; 2nd:14%; 3rd: 10%	HB and wasp	No severe systemic reactions in any group
Laurent et al. 1997 [97]	97	Rush	27%	HB, wasp and Polistes	Adrenaline not needed in any one
Bernstein et al. 1994 [104]	52	Cluster	5.2%		50 μg over 2–3 h on day-1 and maintenance dose achieved over 3 weeks.
Bernstein et al. 1989 [103]	33	Cluster	12%		50 μg over 2–3 h on day-1 and maintenance dose achieved over 3 weeks.
Berchtold et al. 1992 [102]	52	Rush	67%	HB	DBPC study with terfenadine and placebo premedication. Terfenadine group reduced local and cutaneous systemic reactions only, no effect on cardio-respiratory symptoms
Sturm et al. 2002 [98]	101	Rush	7%	HB, YJ and Hornet	More systemic reactions with HB
Birnbaum et al. 2003 [100]	258 (51 children, 201 adults)	Ultra-rapid (50 μg, day-1, 2 doses of 50 μg on day-15 and one 100 μg injection on day-45	11%	HB, YJ, Wasp	More systemic reactions with HB (30%) than YJ (3%) and wasp (6%)
Ewan & Stewart 1993 [152]	26 (727 injections)	Conventional prospective study	23% wasp 10% bee 1.1% severe requiring parenteral treatment	Bee and wasp	Most SR within 30 min. Severe – 3 (0.5%) requiring adrenaline, early onset at 3, 7 and 17 min Mild SR common. Late SR > 2 h were mild: rhinitis and minor urticaria.
Youlten et al. 1995 [153]	109 (2735 injections)		7.5% initial 2.1% maintenance	Bee and wasp	80% within 30 min, 90% within 1 h. 5.5% > 2 h
Hunt et al. 1978 [44]	59 patients, three treatment groups including placebo, whole body extract (WBE) and venom	Single-blind placebo-controlled study; first dose 0.1 μg, 10-fold dose increase every 30 min until 10 μg is reached or patient develops systemic or large local reaction. Subsequent weekly doubling dose increments	No reported systemic reactions	Bee and Wasp	Sting Challenge: 1. Venom group: 5% urticaria only 2. WBE group: 69% SRs 3. Placebo group: 58% SRs
Muller et al. 2002 [154]	52, 26 patients premedicated with terfenadine and 26 with placebo during induction phase	Double-blind placebo-controlled study, rush protocol in 4 days	No reported systemic reactions	Bee venom	–

HB, honey bee; YJ, yellow jacket; VIT, venom immunotherapy.

Antihistamine pre-medication. Pre-medication with anti-histamine before injection in rush immunotherapy reduces the frequency and severity of local and mild SRs [101, 102, 110] but not anaphylaxis. A recent study in patients undergoing bee venom VIT did not confirm the enhancement of efficacy with antihistamine pre-medication as previously suggested [111]. Therefore, it is worth considering antihistamine prophylaxis in those who repeatedly experience local or mild SRs to VIT.

Venom immunotherapy and β-blockers. β-blockers inhibit some of the pharmacological effects of endogenous as well as exogenously administered adrenaline in anaphylaxis and enhance the end organ effects of released mediators. One study reported that patients on β-blockers were nine times more likely to be hospitalized after anaphylaxis to radio-contrast medium (RCM) suggesting a more prolonged and severe reaction [112]. Therefore, β-blockade can make anaphylaxis more protracted and difficult to treat [20, 113]. Hence, caution should be exercised when undertaking allergen-specific immunotherapy in patients on β-blockers and only considered in exceptional circumstances.

In patients with hypertension, β-blockers should be ideally replaced with alternative agents before commencement of VIT.

If co-morbid cardiac conditions are present withdrawal requires careful consideration and discussion with the patient's cardiologist or general practitioner. If a risk-benefit analysis suggests treatment with a β-blocker is essential, appropriate measures should be put into place to mitigate the additional risk and only patients with severe venom allergy considered for VIT [114].

If β-blockers are continued, VIT must be carried out cautiously. Glucagon activates adenyl-cyclase without involving the β-receptor on the cell membrane [115, 116]. Therefore, glucagon should be available and administered promptly if the patient fails to respond to adrenaline in anaphylaxis. Another strategy to consider would be to withdraw β-blockade during up-dosing and recommence after the patient has reached the maintenance dose.

Venom immunotherapy and angiotensin-converting enzyme inhibitors. Case reports raised concern about the concurrent use of ACE inhibitors in patients undergoing VIT [117]. Until recently no studies had reported on patients taking ACE inhibitors during VIT. However, in a retrospective study over 6 years of 79 patients undergoing VIT, 17 had been on ACE inhibitors for a mean of 72 months. During VIT there were no SRs in these patients compared with a SR rate of 21% in the other 62 patients [118].

Venom immunotherapy and anti-immunoglobulin E. There are case reports of anti-IgE therapy with omalizumab reducing the risk of SRs during induction of VIT in patients who have either failed treatment or in those with mastocytosis [119, 120]. However, there are no data on dose regimens, or duration of treatment and current NICE guidelines in the United Kingdom on the use of omalizumab do not allow its use in VIT. Therefore although not recommended, anti-IgE therapy is a strategy that could be considered in exceptional cases.

Venom immunotherapy and mastocytosis. In mastocytosis uncontrolled proliferation of mast cells occurs in tissue thus pre-disposing to severe anaphylaxis as well as exaggerated responses to exogenous insults such as drugs (e.g. aspirin, non-steroidal anti-inflammatory drugs, RCM) and insect stings. Even in relatively milder variants of mastocytosis, insect stings may induce severe anaphylaxis [23, 24]. However, VIT is only recommended for patients with a SR and raised baseline tryptase in the presence of specific IgE. The available data are conflicting on how well VIT is tolerated by patients with indolent forms of systemic mastocytosis and urticaria pigmentosa [25, 69]. The two reported studies involved relatively small cohorts of patients with indolent mastocytosis and employed both conventional and cluster up-dosing protocols. While Bonadonna et al. [69] did not pre-medicate with antihistamine, Gonzalez de Olano et al. [25] pre-medicated a significant proportion of their patients. It is difficult to assess the efficacy and safety of VIT in mastocytosis based on the data from these two small but important studies. Nevertheless, based on the data from the latter two reports and other relatively smaller case series it has been suggested that VIT should be carried out cautiously in this group of patients [121]. Furthermore, as the safety of accelerated VIT protocols has not been clearly established in those with mastocytosis, up-dosing with conventional schedules is recommended.

Currently, there are no data available on the long-term efficacy of VIT in patients with mastocytosis. In view of the severe pre-VIT anaphylaxis to field stings in this group, some authors have advocated continuation of VIT indefinitely if well tolerated [25, 69] although in the United Kingdom the standard recommendation is for 3 years treatment and for these patients to continue to carry emergency treatment including adrenaline.

Patients with a history of a SR but who lack specific IgE, should not be offered VIT but require emergency management and provision of an adrenaline auto-injector.

When to discontinue venom immunotherapy. In UK practice, a duration of 3 years for VIT is recommended [51, 122–124]. There are no specific biomarkers that can reliably assess how long to continue in individual cases. There are also conflicting views with Mueller proposing that a negative IDT at the end of VIT predicts long-term protection [124] and Golden suggesting continuing risk despite negative skin test [125]. Live sting challenges are not recommended in routine clinical practice for assessment of treatment success since they have poor reproducibility [62, 122, 126, 127].
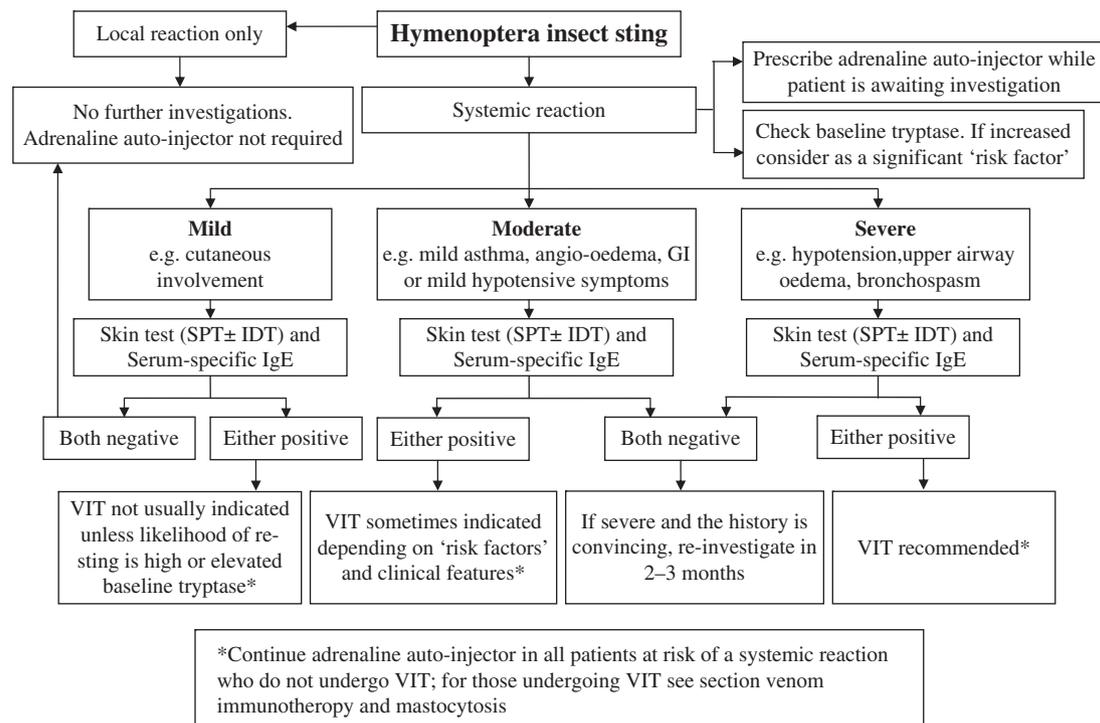
Fig. 2. Schematic representation of diagnosis and management of hymenoptera venom allergy (bee and wasp venom). IDT, intradermal testing; SPT, skin prick test; VIT, venom immunotherapy.

The majority of patients at the end of 3–5 years of VIT have detectable specific IgE despite being protected from future stings [124]. Long-term follow-up studies have shown that the cumulative risk for SRs is 5–15% in adults and at least 5% in children after 5–13 years and 10–15 years off VIT, respectively [51, 122, 124]. Although one study suggested a longer duration of VIT was associated with fewer relapses, confounding factors were that most (80%) were bee allergic and baseline tryptase status was unknown [124]. There was also a very high re-sting rate (62%) unlike that in United Kingdom.

VIT administered indefinitely has been proposed in patients with mastocytosis on the basis of four deaths [128–130]. However of these four patients at least one, and probably two, who died after discontinuing bee VIT, were stung by a wasp. The third patient failed immunotherapy, which was then discontinued after 2.5 years, following allergic reactions during VIT, a field sting and skin testing. In the fourth patient, VIT was successful in that venom-specific IgE became negative, so the death is attributable to the mastocytosis rather than the IgE-mediated component of the disease. Hence there is no evidence to support indefinite VIT in mastocytosis and this cannot be recommended in the United Kingdom without further evaluation [108, 121, 128–130].

Who should carry an adrenaline autoinjector following venom immunotherapy. All patients undergoing VIT should carry an adrenaline auto-injector during up-dos-

ing. Although not evidence-based, BSACI also recommends that the following groups are provided with an adrenaline autoinjector even after successful up-dosing and completion of VIT:

1. Those at continuing risk of multiple stings, for example a gardener with an occupational risk of multiple wasp stings or a beekeeper after bee VIT.
2. If during immunotherapy the patient continued to experience allergic reactions.
3. Patients with an elevated baseline tryptase or mastocytosis.

Effect of venom immunotherapy in children

VIT reduces the frequency and severity of SRs among children who have previously had moderate-severe SRs [45, 51]. The prolonged benefit is greater than that seen in adults and persists for many years after stopping treatment [51, 52].

A schematic pathway for the management of hymenoptera venom allergy is shown in Fig. 2.

Practical aspects of venom immunotherapy

As with other forms of immunotherapy, safety measures are paramount. VIT should be carried out only by a specialist with experience and knowledge in this field. Children should undergo skin testing and receive immunotherapy in the same way as adults. Shorter induction protocols such as rush and ultrarush protocols can be used

to reduce the number of hospital visits, but their use must be limited to specialist centres [131].

Safety measures

a. *Assessment of a patient before injection*: Before each injection the patient should be asked a series of questions. Establish if there were any late-reactions (systemic or large local) to the last injection and if so the nature, severity, time of onset and treatment. Enquire if stung during the interval and if so the nature of any reaction.
b. *Pre-treatment measurements*: Measure baseline pulse, blood pressure and peak expiratory flow rate (PEFR). With accelerated protocols check pulse, blood pressure and PEFR at baseline and before each dose escalation step.
c. *Administration of correct allergen and dosage*: The name and identity of the patient must be checked before administration of the injection.
d. Any changes in the patient's medical status (e.g. having been diagnosed with a cardiac/respiratory condition; commencement on a β-blocker or other medication) should be enquired before each injection.
e. Injections should not be administered if the patient has an intercurrent infection, particularly those affecting the respiratory tract or during sepsis.
f. The correct venom, dosage and shelf life of the product should be checked by two health professionals experienced in VIT before administration.
g. Although not mandatory, it is good clinical practice to document the batch number of the product that has been administered in the patient's hospital records.
h. Injections must be given by the subcutaneous route and appropriate precautions taken to ensure that the venom is not given intravascularly.
i. Patients must be observed for a minimum of 60 min following each injection. It is important to ensure that the patient is well before discharge including measurement of PEFR (pulse and blood pressure where appropriate) and documentation of local reactions.

A VIT questionnaire for assessment before VIT injections is shown in Appendix C.

Dosage adjustment

a. This is necessary when patients miss scheduled injections during the induction and maintenance phases.
b. In the event of LLR (>10 cm), a dose reduction to the previous tolerated dose in the initial course is recommended. In patients with recurrent troublesome local reactions, pre-medication with an antihistamine should be considered or the dosage split between different sites.
c. In patients developing SRs to VIT, the subsequent dose should be reduced (depending upon the severity of the reaction) followed by careful dose escalation and pre-medication with antihistamine considered.

Mechanism of venom immunotherapy

VIT exerts its effects by modulating both T and B cell responses to allergen [132]. The early production of IL-10 and induction of T cell 'anergy' appears to be the key event in this process [133–135]. Allergen immunotherapy has been shown to increase production of IL-10 by antigen presenting cells, including B cells, monocytes and macrophages, a phenomenon that might lead to the increased generation of IL-10 secreting T regulatory cells (CD4(+)CD25(+)Foxp3(+) cells) [134, 136]. Furthermore, increased production of TGF-β has also been reported following allergen immunotherapy and has been shown to contribute to regulatory T cell function. IL-10 initiates T cell 'anergy' or 'hyporesponsiveness' to venom by blocking tyrosine phosphorylation of CD28 and inhibiting CD28 co-stimulatory signal [137, 138].

VIT induces an early shift in the Th1/Th2 balance, i.e., there is a change from a Th2 to Th1 dominant pattern [139]. With rapid VIT initiation protocols, there was a marked reduction in *in vitro* proliferation of peripheral blood mononuclear cells to venom and IL-4/IL-5 production together with an increased generation of IFN-γ and IL-10 within days [139, 140]. Addition of anti-IL-10 antibodies to cell cultures prevented the downregulation of venom-induced proliferation showing that IL-10 played a key role in T cell 'anergy' or 'hyporesponsiveness' [134]. Also, there is some evidence that IL-10 inhibits IgE-dependent mast cell activation, which may explain the efficacy of VIT despite the continued detection of venom-specific IgE in most patients at the end of the treatment phase [141].

VIT is also associated with an increase in venom-specific IgG4 and a gradual decrease in specific IgE, with a consequent increase in IgG4 : IgE ratio [142–145]. The increase in venom-specific IgG4 after VIT is greater in wasp-allergic patients compared with bee-allergic patients although no correlation was found between reactions to sting challenges and venom-specific IgG4, IgE or IgG4 : IgE ratio [142–145].

Future research areas

1. Epidemiological studies to determine the prevalence of hymenoptera venom allergy in United Kingdom.
2. Natural history of venom allergy in patients not undergoing VIT.
3. Investigation of the role of recombinant allergens in enhancing the sensitivity and specificity of diagnostic testing in hymenoptera venom allergy.
4. Studies to investigate the efficacy, safety and duration of VIT in patients with increased mast cell load.

5. Feasibility of sublingual VIT and other routes of administration including a direct intralymphatic approach.
6. Prospective controlled studies to assess safety and efficacy of standardized aqueous and depot venom extracts.
7. Newer approaches for VIT including using modified recombinant allergen, T cell epitopes and DNA vaccination.
8. Studies on the role of anti-IgE during up-dosing to reduce reactions.
9. Studies on the role of antihistamine pre-medication.
10. Effect of VIT on QOL in children.

Acknowledgements

These *guidelines* inform the management of venom allergy. Adherence to these guidelines does not constitute an automatic defence for negligence and conversely non-adherence is not indicative of negligence. It is anticipated that these guidelines will be reviewed 5 yearly.

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Appendix A: Measures to avoid hymenoptera stings

a. Wear light coloured clothing.
b. Avoid strong fragrances, perfumes and highly scented shampoos.
c. Wear shoes while outdoors and cover body with clothing, cap/hat and use gloves while gardening.
d. Avoid picking fruit from the ground or trees. Exercise caution in gardens, picnic areas and outdoors where food is served and near refuse.
e. Avoid drinking out of opened drink bottles/cans to prevent being stung inside the mouth.
f. Wash hands after eating or handling sticky or sweet foods outdoors (especially children)
g. Keep uneaten foods covered especially when eating outdoors.
h. Avoid high-risk hobbies if possible, e.g. bee keeping in bee venom allergic subjects.
i. Always contact professionals to remove bee or wasp nests.
j. Wear full protective clothing while handling bees.
k. For bee keepers: to avoid family members being stung, the beehives should be kept away from the house and bee keepers advised to change clothing before entering their home. Honey extraction at home increases the risk of being stung.

Appendix B: Examples of venom immunotherapy protocols

Tables B1–B3

Table B1. Conventional VIT

Week no.	Dosage micrograms of bee or wasp venom subcutaneously
1	0.01*
2	0.1
3	1.0
4	5
5	10
6	20
7	30
8	40
9	50
10	60
11	80
12	100

*May be lower depending on patient's sensitivity.
As per manufacturer's recommendation – ALK Pharmalgen Bee and Wasp venom; for a more detailed description refer to the manufacturer's product information.

Table B2. Rush VIT

Day no.	Dosage micrograms of bee or wasp venom subcutaneously
1	0.001
	0.01
	0.1
	0.2
	0.4
2	0.8
	1.0
	2.0
	4.0
	6.0
3	8.0
	10
	20
	40
	60
4	80
	100

Injections in 60-min intervals on each day [98].

Table B3. Ultra-rush VIT [99]

Day no.	Dosage micrograms of bee or wasp venom subcutaneously
1	0.01
	0.1
	1.0
	10
	20
	40
	80
2	100
	100

Nine injections over 2 days; Day 1: seven injections at 30–60 min intervals; Day 2: two injections at 2–4 h interval; days 1 and 2 as in-patient; maintenance dose of 100 μg given on days 7, 14, 28, 42, 63, 84 and then monthly as out patient [99].

Appendix C: Assessment before venom immunotherapy

History required before each injection to decide if suitable to proceed or if dose modification required

Did you have a large local reaction to the last injection?	**Yes/No**
If you said yes to the above question: How large was this reaction and how long did it last? _____	
Did you have any reaction to the last injection after leaving the clinic?	**Yes/No**
Have you been stung since your last injection?	**Yes/No**
If you said yes to the above question: Which insect stung you? Was it a full sting, partial sting, single sting or multiple stings? What was the outcome? _____ _____	
Have you had a 'cold', 'chest infection', or other infection in the last week?	**Yes/No**
Have you been diagnosed with any new illness recently?	**Yes/No**
Have there been any problems with your asthma control since your last injection?	**Yes/No**
Do you have any other active allergy?	**Yes/No**
Have you changed your medicines since your last injection	**Yes/No**