Low-Dose Oral Food Challenge with Hazelnut: Efficacy and Tolerability in Children

GUIDELINES

Hymenoptera Venom Allergy: Management of Children and Adults in Clinical Practice

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Abstract

Hymenoptera venom allergy is an epidemiologically underestimated condition and a major cause of morbidity worldwide. Preventing future allergic reactions in patients who experience a systemic reaction is based on the correct management of the emergency followed by an accurate diagnosis, prescription of adrenaline autoinjectors, and, where indicated, specific venom immunotherapy. Some epidemiological studies highlight our poor knowledge of this disease and the frequent inadequacy of its management. Moreover, they emphasize the importance of such a life-saving treatment as specific immunotherapy. The availability of high-quality hymenoptera venom extracts for diagnostic and therapeutic use has dramatically improved the prognosis and quality of life of allergic patients. Subcutaneous venom immunotherapy is currently the most effective form of allergen-based immunotherapy, with a carry-over effect lasting up to several years after its interruption. This report on the management of hymenoptera venom–allergic children and adults was prepared by a panel of Italian experts. The main objective of this consensus document is to review the scientific evidence related to diagnosis, therapy, and management of patients allergic to hymenoptera venom. Thus, we can improve our knowledge of the disease and promote good clinical practices. The present document provides practical suggestions for correct diagnosis, prescription of emergency therapy and immunotherapy, and strategies for patient care.

Key words: Adults. Children. Diagnosis. Efficacy. Hymenoptera. Immunotherapy. Management. Safety.

Resumen

La alergia al veneno de himenópteros es una condición subestimada epidemiológicamente que representa una causa importante de morbilidad en todo el mundo. La prevención de reacciones alérgicas futuras en pacientes que han desarrollado una reacción sistémica se basa en el manejo correcto de la emergencia, seguido de un diagnóstico correcto, la prescripción de autoinyectores de adrenalina y, en el caso de estar indicada, la prescripción de inmunoterapia específica con veneno (VIT). Varios estudios epidemiológicos destacan el escaso conocimiento de esta enfermedad y un frecuente tratamiento insuficiente. Además, enfatizan la importancia de la inmunoterapia específica, un tratamiento que puede salvar la vida del paciente. La disponibilidad de extractos de veneno de himenóptera de alta calidad para uso diagnóstico y terapéutico ha mejorado drásticamente el pronóstico y la calidad de vida de estos enfermos. La VIT subcutánea representa la forma más efectiva de inmunoterapia con alérgeno actualmente disponible, con una eficacia persistente que dura hasta varios años después de su interrupción. Este consenso sobre la evaluación clínica tanto de niños como de adultos alérgicos al veneno de himenópteros ha sido elaborado por un panel de expertos italianos. Su objetivo principal es revisar la evidencia científica disponible en el diagnóstico, la terapia y la evaluación clínica de los pacientes alérgicos al veneno de himenópteros con el propósito de mejorar el conocimiento sobre esta enfermedad y promover buenas prácticas clínicas. Se incluyen sugerencias prácticas para un diagnóstico correcto, la prescripción de terapia de emergencia e inmunoterapia, así como estrategias para el manejo de los pacientes.

Palabras clave: Adultos. Niños. Diagnóstico. Eficacia. Himenópteros. Inmunoterapia. Tratamiento. Seguridad.

Introduction

Hymenoptera venom allergy is an epidemiologically underestimated condition and a major cause of morbidity worldwide. Mortality is low, although underestimates are common, with many sting fatalities being misdiagnosed. Preventing future allergic reactions in patients who have developed a systemic reaction is based on correct management of the emergency followed by diagnosis, prescription of adrenaline autoinjectors, and, where indicated, specific venom immunotherapy (VIT). Some epidemiological studies highlight our poor knowledge of this disease and the frequent inadequacy of its management [1] and emphasize the importance of such an important life-saving treatment as specific immunotherapy.

The availability of high-quality hymenoptera venom extracts for diagnosis and therapy has dramatically improved the prognosis and quality of life of allergic patients. Subcutaneous VIT is currently the most effective form of allergen-based immunotherapy, with a carry-over effect lasting up to several years after its interruption.

This report on the management of hymenoptera venom allergy was prepared by a panel of Italian experts.

Objectives and Work Methodology

The main objective of this consensus is to review scientific evidence associated with the diagnosis, treatment, and management of patients who are allergic to hymenoptera venom and thus to improve our knowledge of this disease and promote good clinical practice. This document provides practical suggestions for correct diagnosis, prescription of emergency therapy and immunotherapy, and strategies for the care of patients.

The data on the various topics addressed in this report were obtained from studies published in English and Italian and collected by searching the MEDLINE and EMBASE databases. The GRADE system was used for translating research results into recommendations based on scientific evidence (Table 1) [2]. We included all recommendations for which agreement was by ≥90% of the authors. The panel of experts comprised physicians with broad experience in hymenoptera venom allergy working in one of the main allergy centers. Some centers started administering VIT in the early 1980s.

Hymenoptera Venom Allergy: Epidemiology and Clinical Picture

Hymenoptera

The insects of the order of Hymenoptera comprise aculeate species whose venom can trigger allergic reactions in humans. These reactions range from relatively mild reactions to fatal anaphylaxis [3]. In Europe, hymenoptera causing allergic reactions belong to the Apidae and Vespidae families or, sporadically, to Formicidae (*Formica rufa*) [4] and Myrmicinae (*Solenopsis invicta*) [5], which are widespread in North and Central America and in Australia.

The Apidae family includes the subfamilies Apinae (*Apis mellifera*) and Bombinae (*Bombus terrestris, agrarum, medics*), while the Vespidae family is composed of the Vespinae subfamily, including the genera *Vespula* (*germanica, vulgaris*), *Dolichovespula* (*maculata, arenaria, saxonica, media*), and *Vespa* (*crabro, orientalis velutina var nigrithorax*) and the subfamily Polistinae, which includes the genus *Polistes* (*dominula, gallicus*).

The bees and vespids of the genus *Vespula* are widespread in the far northern regions of Europe. In southern Europe, in addition to *Vespula*, hornets are a frequent cause of allergic reactions (genus *Vespa*), including the most widespread species *Vespa crabro* and some species of *Polistes*, such as *Polistes dominula* [6]. The genus *Dolichovespula* has a more limited diffusion and can be considered similar to *Vespula* from an allergological point of view.

In 2005, *Vespa velutina nigrithorax*, which is from Southeast Asia, was detected in the South of France. *Vespa velutina* is a predator of bees and is rapidly spreading from

Table 1. Levels of Evidence and Grade of Recommendation [2]

Level of Evidence	
Level I	Systematic reviews, meta-analysis, randomized control trials
Level II	Two groups, nonrandomized studies (eg, cohort, case-control)
Level III	One group nonrandomized (eg, before and after, pretest and posttest)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V	Case reports and expert opinion that include narrative literature, reviews, and consensus statements
Grade of Recommendation	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level

France to neighboring countries. Anaphylactic reactions have been reported after *Vespa velutina* stings, with a variable degree of cross-reactivity with other vespids [7].

Given its low aggressiveness, allergy to bumblebees concerns a limited number of persons, in particular professionally exposed individuals [8], and should therefore be investigated on the basis of a detailed clinical history, provided that a suitable extract is commercially available for diagnosis. Immunotherapy with honeybee venom alone may be sufficient in non–professionally exposed bumblebee-allergic patients with primary sensitization to bee venom, whose reaction is most likely due to cross-reactivity. In occupationally exposed patients, who are frequently stung by bumblebees, immunotherapy should be with purified bumblebee venom (when available) [9].

Although difficult, recognition of the stinging insect remains crucial in the management of allergic reactions and is an integral part of the diagnosis in that it helps us to select specific immunotherapy; thus, information on the behavior and morphological characteristics of the culprit insects make for an accurate clinical history and diagnosis.

A mellifera has a characteristic serrated sting which remains stuck in the tissue together with the venom sack. The bee dies by self-evisceration when flying away from the victim. The vespids and other apids (bumblebees), on the other hand, have smooth stings, which can be extracted from their victims, thus enabling them to sting several times consecutively.

Epidemiology

Depending on the living environment and type of activity, 56%-94% of the adult population are estimated to have been stung by a hymenoptera insect at least once in their lifetime; in Europe, this is by a bee in about one-third of cases [10]. As a consequence, the development of specific IgE to 1 or more venom allergens can occur as an ancestral defense response against the toxic effects of venom [11]. Such a response may be favored by atopic diathesis and genetic factors and may correlate with a high level of total IgE [10,12].

The prevalence of asymptomatic sensitization is estimated to range from 9.3% to 40.7% in the adult population, with higher proportions in cases of high exposure, for example, beekeepers (30%-60%) [13,14].

Epidemiological studies report wide variability in the prevalence of allergic reactions: repeated exposure to stings (studies on beekeepers) increases the prevalence of a large local reaction (LLR) by as much as 38% [15] and that of systemic reactions by 30%-45% [16,17].

In Europe, the prevalence of systemic reactions in the adult general population is 0.3%-8.9% [10,18], which increases to 14%-32% among beekeepers [13]. Taking into account studies on anaphylaxis as a whole, hymenoptera stings are responsible for 7.3%-59% of cases, depending on the populations investigated, and are more frequent in adults [15].

According to data from the European Anaphylaxis Registry, out of 3333 diagnosed cases, hymenoptera venom allergy was the most frequent cause of severe reactions in the adult population (48.2%) [19].

Data from emergency departments in several parts of the world show that hymenoptera venom allergy is responsible for 1.5%-34% of anaphylactic reactions, with the lowest prevalence recorded in urban hospitals [10].

Recent Italian studies on cases of anaphylaxis reported directly by emergency departments to allergy centers for diagnostic assessment have shown that hymenoptera venom allergy is the most frequent cause (42%-70% of cases) [20,21].

Hymenoptera venom allergy is responsible for about 20% of the total cases of fatal anaphylaxis in several countries [10]. Death is due to shock with multiple organ failure within 10-15 minutes of the sting and, in a quarter of cases, edema of the glottis [22].

Overall, the incidence of mortality in various European countries is between 0.03/million/year in Italy and 0.48 in France. In Italy, ISTAT data for the period 1994-2003 show 94 deaths [15]. Mortality data are generally underestimated, as deaths are likely to be attributed by mistake to other causes, in particular cardiac disorders [10].

Since 40% of cases of fatal anaphylaxis occur as a first reaction to hymenoptera venom, it is important to carefully evaluate the risk factors that may cause a transition from asymptomatic sensitization to a more severe clinical manifestation [10,23-26].

Clinical Aspects

Hymenoptera venom is a mixture of various components, including bioactive molecules such as histamine, serotonin, tyramine, catecholamines, low-molecular-weight peptides (including mastoparans, kinins, and chemotactic peptides), and high-molecular-weight proteins (including phospholipase, hyaluronidase, mellitin, antigen 5), which differ by species and can act as allergens and, in some cases, cause toxic reactions.

From a clinical point of view, we can distinguish between local reactions, LLRs, systemic allergic reactions, toxic systemic reactions, and unusual reactions.

In most cases, local reactions consist of itching, erythema, and edema of limited extension; they are transient, normal consequences of the vasoactive and inflammatory action of some venom components. In the event of allergy, more severe large local reactions may occur, and these are characterized by delayed and prolonged inflammation and edema increasing within 24-48 hours and resolving in 3-10 days, with an average extension exceeding 10 cm in diameter.

The anaphylaxis guidelines of the World Allergy Organization [27] and of the European Academy of Allergy and Clinical Immunology (EAACI) [28] have established clinical criteria for the diagnosis of anaphylaxis, confirming the proposal of the second symposium on the definition and management of anaphylaxis summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium [29].

Various classifications of the grade of severity of reactions have been proposed, those of Mueller [30] and Ring and Messmer [31] being the most frequently referred to. Both classifications have limitations: that of Mueller does not take into account the possible absence of cutaneous symptoms and the possibility that an isolated cardiovascular shock might be the only allergic sting-induced manifestation [29], while that of Ring and Messmer is almost entirely focused on cardiovascular collapse, which is considered more severe than respiratory impairment.

The classification of mild, moderate, and severe reactions of Brown [32] can also be adapted to systemic allergic reactions to hymenoptera venom [33]. EAACI recently proposed a simplification of the severity criteria for acute allergic reactions, dividing them into local (grade 1) and systemic (grades 2 and 3) [34].

Skin symptoms are the most frequent manifestation (80%) and represent the only manifestation in 15% of cases of systemic reactions in adults. Some cases are characterized by onset of chronic urticaria and cold urticaria after the sting, generally without an immediate reaction and with an unknown risk for systemic reactions to re-sting. Almost 50% of systemic reactions include respiratory symptoms (upper airway angioedema). Symptoms and signs of hypotension may appear in over 60% of adults; in half of the cases, these occur with loss of consciousness. Cardiac involvement during anaphylaxis can cause bradycardia, arrhythmias, and acute coronary syndromes, thus making it compatible with Kounis syndrome [35,36]. It can also be secondary to decreased venous return, which is in turn due to histamine-induced vasodilatation, and permeabilization. Gastrointestinal symptoms (abdominal pain, nausea, vomiting, and diarrhea) and uterine cramps with possible miscarriage may occur, as may neurological symptoms (eg, convulsions). Biphasic anaphylaxis, which is characterized by recurrence of anaphylactic symptoms within 4-12 (exceptionally 72) hours [37] after resolution (without re-exposure), was reported in 0.4%-14.7% of cases [38].

Toxic systemic reactions are caused by the action of venom components with enzymatic activity and organ-specific toxicity and usually occur after multiple simultaneous stings (from several tens to several hundreds). Toxic effects occur in hours to days and consist of rhabdomyolysis, intravascular hemolysis, coagulation disorders, liver damage, and acute renal failure. Fatal cases are uncommon [39].

Unusual reactions are rare and are caused by a toxic or non–IgE-mediated immunological mechanism, in some cases by autoimmunity. These can occur within hours to days of a single sting and include serum sickness–like manifestations, central nervous system manifestations (acute encephalopathy, Guillain-Barré syndrome, myasthenia, peripheral neuritis), hematological reactions (thrombocytopenic purpura, Henoch-Schönlein purpura, hemolysis, coagulation disorders), muscle reactions (rhabdomyolysis), renal reactions (acute renal failure due to interstitial nephritis or tubular damage, nephrotic syndrome), and respiratory reactions (alveolar hemorrhage) [40]. Metrorrhagia after a bee sting is unusual [41].

Pediatric Aspects

The prevalence of asymptomatic sensitization was reported to be 3.7% in an Italian pediatric case study [42]. The prevalence of LLRs has been reported to be between 0.9% [43] and 20.8% [44]; the prevalence of systemic reactions is below 1% [15,42].

According to the European Anaphylaxis Registry, hymenoptera venom allergy is the second cause of severe reactions in children (20.2%) after food allergy [19].

Risk factors for severe systemic reactions after hymenoptera stings in children were evaluated by Graif et al [45] in a population of adolescents aged 13-14 years. Atopic children had a significantly higher rate of severe reactions than nonatopic children (36.9% vs 24.8%). Therefore asthma, allergic rhinitis, and atopic eczema should be considered risk factors for reactions of any severity; moreover, the severity of the reaction is also associated with the severity of asthma. Atopy was confirmed as a risk factor for severe reactions in a more recent study [46]. However, this finding should be confirmed in larger pediatric populations.

In children, systemic reactions mostly affect the skin and rarely the cardiovascular system. Skin symptoms are the only clinical manifestation in 60% of cases [47].

Children have a favorable prognosis regarding re-sting, both in studies based on sting challenge [48] and field sting [49,50].

Treatment of Acute Reactions

In the Hospital Setting

Treatment of anaphylactic reactions in the hospital setting should adhere as closely as possible to guidelines. After discharge, the patient should be referred to an allergy specialist and prescribed adrenaline autoinjectors [51-53]. As for postanaphylaxis monitoring, WAO guidelines indicate a minimum of 8-10 hours to cover the risk of late anaphylactic reactions [27]. American guidelines [54] suggest individualizing this period, whereas the EAACI guidelines [28] advise a minimum duration of 6-8 hours for patients with respiratory symptoms and 12-24 hours in the event of hypotension or collapse.

The expert panel believe that, after appropriate therapy and complete resolution of the clinical picture, the patient should

be kept under observation and monitored for at least 6-8 hours up to 24 hours depending on the severity and characteristics of the reaction at onset, comorbidity, and risk factors (strength of recommendation, D). The duration of this period may depend on the internal regulations of the individual hospital.

Management of anaphylaxis in the hospital setting requires general measures and the administration of specific medicinal products [27].

General measures include the following: (*a*) Monitoring of vital parameters. (*b*) Positioning of the patient in the Trendelenburg position (supine with legs raised 10°-15°) or, in the case of vomiting, on the right side. If the patient is pregnant, she should be placed in the supine position to gently dislodge the fetus to the left so as to decompress the inferior vena cava and thus improve venous return to the heart; if she is laid on one side, it should be the left. (*c*) Rapid cannulation of a peripheral venous access with a high-gauge needle (at least 18 G). (*d*) Rapid intravenous administration of isotonic saline solution (plasma expanders should be avoided owing to the risk of mast cell degranulation). (*e*) Administration of oxygen (if necessary); in the case of pregnancy, oxygen should be administered to avoid fetal hypoxemia (4 L/min using nasal prongs). (*f*) Continuous clinical and instrumental monitoring of the patient (arterial blood pressure, heart rate [bradycardia in hypotension seems to have a negative prognostic value], and peripheral oxygen saturation).

The specific medicinal products used in the management of anaphylaxis are as follows:

– *Adrenaline:* Adrenaline is the treatment of choice for anaphylaxis regardless of the presence of shock (strength of recommendation, C) [27-29,55,56]. It slows the progression of symptoms and can prevent the development of fatal or biphasic reactions (strength of recommendation, C) [57,58]. If the correct dosage is administered, it can be used without absolute contraindications in pediatric and geriatric populations and in patients with heart disease [28,59,60], except for some conditions, such as long QT syndrome (in this case, adrenaline should be administered with extreme caution, in the case of real need, and in the presence of the cardiologist).

  Adrenaline is also the drug of choice for the treatment of anaphylaxis in pregnant women (strength of recommendation, D) [61-63]; in fact, ephedrine may have a lower risk of uterine contractions, although if it proves inefficacious, it may cause escalation of the anaphylactic reaction, with the consequent risks.

  Adrenaline should be administered intramuscularly in the lateral thigh (vastus lateralis muscle) at a dose of 0.01 mg/kg of a 1/1000 solution, with a maximum dose of 0.3 mg in children and 0.5 mg in adults [27]. The dose may be repeated after 5-15 minutes if necessary (strength of recommendation, B) [27,59].

  Intravenous administration should be reserved for the most severe cases, with imminent danger of life for cardiovascular collapse (strength of recommendation, D) [56,64]. The infusion should be stopped 30 minutes after clinical stabilization. Table 2 describes the modalities and the concentrations of intravenous adrenaline.

Table 2. Intravenous Administration of Adrenaline

Bolus
1 ampoule diluted to 10 mL (100 µg/mL) → 0.5 mL (=50 µg) in bolus or syringe pump
1 ampoule diluted to 50 mL (20 µg/mL) → 180 mL/hour for 1 minute
Infusion in syringe pump
1 ampoule of 1 mg, diluted to 50 mL with saline solution speed = 20 µg/mL
Infusion rate in syringe pump: 5 µg/min 15 mL/h 10 µg/min 30 mL/h 15 µg/min 45 mL/h

Table 3. Dopamine: Hourly Rate of Administration Based on Body Weight and Desired Dosage[a]

Body	5 µg/kg/min		10 µg/kg/min		15 µg/kg/min	
	µg/min	mL/h	µg/min	mL/h	µg/min	mL/h
40	200	1.50	400	3.00	600	4.50
50	250	1.87	500	3.75	750	5.62
60	300	2.25	600	4.50	900	6.75
70	350	2.62	700	5.25	1050	7.87
80	400	3.00	800	6.00	1200	9.00
90	450	3.37	900	6.67	1350	10.12

[a]200-mg ampoule: 2 ampoules in 5% glucose solution administered using a 50-mL syringe pump (=8000 µg/mL).

– *Dopamine:* Dopamine should be used if it is not possible to maintain stable circulatory function with adrenaline. The dosage is 5-15 µg/kg/min. Table 3 shows the hourly infusion rate using a syringe pump for the desired dosages based on body weight.

– *Antihistamines:* The use of anti-H_1 is recommended only for the treatment of skin symptoms (strength of recommendation, B) [28,65,66]. There are no controlled studies to support the use of antihistamines for the treatment of anaphylaxis [67]. Intravenous administration has the advantage of acting more quickly, although it should be performed very slowly to avoid adverse effects (including hypotension). The suggested dose is generally 10 mg of chlorpheniramine in adults and 2.5-5 mg in children [27].

  The concomitant administration of anti-H_2 antihistamines has not proved to have greater therapeutic efficacy and is therefore not recommended in guidelines.

– *Corticosteroids:* Corticosteroids are used for the control of bronchospasm and prevention of biphasic reactions [28,54,59,65], even if there are no controlled studies to confirm their effectiveness in the treatment of acute anaphylactic reaction (strength of recommendation, D) [68]. The recommended drugs are intravenous hydrocortisone 200 mg in adults (in children up to 100 mg) or intravenous methylprednisolone

Table 4. Doses of Glucagon to Be Administered During Anaphylaxis

Glucagon Dosage	Syringe Pump Infusion Speed[a]
1 mg/h	50 mL/h
2 mg/h	100 mL/h
3 mg/h	150 mL/h
4 mg/h	200 mL/h
5 mg/h	250 mL/h

[a]1-mg ampoule, diluted to 50 mL with saline solution = 0.02 mg/mL.

50-100 mg in adults (in children 1 mg/kg, maximum 50 mg) [27].

– *Glucagon:* Glucagon exerts both positive inotropic and chronotropic effects for activation of adenylyl cyclase activity independently of the ß receptor. It is sometimes needed in patients taking a ß-adrenergic blocker who have hypotension and bradycardia and who do not respond optimally to adrenaline. Glucagon can be administered intravenously in adult patients at a dose of 1 mg as an initial intravenous bolus; the dose can be repeated every 5 minutes and increased to 3-5 mg if necessary. Continuous infusion in a syringe pump should be at 1-5 mg/h (strength of recommendation, D) (Table 4). It should be pointed out that glucagon is an off-label drug for the therapy of anaphylaxis and can lead to severe vomiting and hyperglycemia [69,70].
– *Desmopressin:* Desmopressin can be used for the treatment of anaphylactic shock that is unresponsive to adrenaline (strength of recommendation, D) [71,72].
– *Bronchodilators:* Inhaled short-acting formulations (eg, salbutamol) are preferred.

Self-treatment

All patients with a history of anaphylactic reaction should be provided with adrenaline autoinjectors to be injected into the vastus lateralis muscle [27,28,73]. Currently available autoinjectors differ from country to country [74]. In obese or overweight patients, the reduced length of the needle does not always ensure intramuscular administration [75,76]; therefore, the patient should be advised to press the autoinjector well into the thigh fat to compress it and allow the adrenaline to penetrate the muscle.

One study compared 3 adrenaline autoinjectors for penetration depth in ballistic gelatin, namely, 2 cartridge-based devices (EpiPen and Jext) and 1 syringe-based device (Anapen) [77]. For the 2 cartridge-based systems, the mean (SD) maximum injection depth in gelatin within 10 seconds was 29.68 (2.08) mm for EpiPen and 28.87 (0.73) mm for Jext; for the syringe-based system (Anapen), the depth was 18.74 (1.25) mm. Cartridge-based systems therefore reached a depth that was double the length of the needle. The same study also showed that the average depth of the adipose tissue in 50 females was 14.8 mm. Comparison of the robustness and performance of these 3 devices revealed that cartridge-based systems are more robust and ensure greater speed, validity, correctness of the dose, and accuracy of the site of administration than the syringe-based system. However, a recent study showed that the bioavailability of adrenaline administered using a syringe-based autoinjector is not affected by needle length [78].

In the pediatric population, considering the fixed dosages of the autoinjector, there is a risk of administering a lower or higher dose, depending on body weight [59,79]. In children weighing 15-30 kg, a lower dose should be used if the anaphylactic reaction is not severe; an adult dose should be administered if the anaphylaxis is severe or the patient has concomitant bronchial asthma (risk factor for fatal anaphylaxis) [80].

Table 5 shows the symptoms and signs indicative of an anaphylactic reaction to ensure that the patient knows when to administer adrenaline; this table can be provided to the patient during training with the device.

Table 5. Criteria for the Diagnosis of Anaphylaxis [27]

Naive patient
Acute onset (minutes or hours) of cutaneous and/or mucosal symptoms (pruritus, flushing, lips-tongue-uvula swollen, hives and generalized urticaria) + One or more of the following: A. Respiratory symptoms (dyspnea, wheezing, bronchoconstriction, stridor, reduced peak expiratory flow, hypoxemia) B. Decreased blood pressure and/or associated symptoms of the target organs (hypotonia, collapse, syncope, incontinence) These criteria allow the diagnosis of about 80% of cases of anaphylaxis, as cutaneous symptoms are present in 80% of anaphylactic reactions
After exposure to a likely allergen
Two or more of the following: A. Cutaneous and/or mucosal symptoms (pruritus, flushing, lips-tongue-uvula swollen, hives and generalized urticaria) B. Respiratory symptoms (dyspnea, wheezing, bronchoconstriction, stridor, reduced peak expiratory flow, hypoxemia) C. Decreased blood pressure and/or associated symptoms of the target organs (hypotonia, collapse, syncope, incontinence) D. Persistent gastrointestinal symptoms (abdominal pain, cramps, vomiting)
After exposure to a known allergen
Reduction in blood pressure: A. Infants and children: <70 mmHg from 1 mo to 1 y <70 mmHg (+2 × y) from 1 to 10 y <90 mmHg from 11 to 17 y B. Adults: <90 mmHg or a decrease >30% from baseline values

Although many patients are afraid to use their adrenaline autoinjector for fear of adverse effects [81], no significant adverse effects have been reported, with the exception of the known onset of tachycardia, tremors, and peripheral vasoconstriction [82].

Even if adrenaline remains the first-choice drug in anaphylactic reactions, the patient with mild systemic reactions (eg, only hives) may also self-treat with oral corticosteroids (eg, methylprednisolone tablets 16 mg = 4 tablets) and a double dose of second-generation antihistamines.

Indications for the Prescription of Adrenaline Autoinjectors

Adrenaline autoinjectors should be prescribed to the following groups of patients [28,33,73,74]:

- Children and adults with systemic reactions more severe than systemic skin reaction or with a high risk of re-exposure to stings (eg, beekeepers), before VIT (level of evidence IV, strength of recommendation C).
- Children and adults undergoing VIT, but with risk factors for incomplete clinical protection (very severe onset reaction, adverse reactions during immunotherapy, lack of sting protection during VIT, bee venom allergy) (level of evidence V, strength of recommendation D).
- Children and adults who have discontinued VIT but present risk factors for incomplete clinical protection (eg, particularly severe pre-VIT systemic reaction, systemic reaction caused by VIT, lack of protection during VIT) (level of evidence V, strength of recommendation D).
- Children and adults with elevated levels of serum mast cell tryptase or mast cell disorders and a history of systemic reaction to hymenoptera sting, independently of VIT (level of evidence IV, strength of recommendation D).
- Children and adults who discontinued VIT, despite having mast cell disorders and/or elevated levels of serum mast cell tryptase (level of evidence IV, strength of recommendation C).

According to European guidelines, the prescription of 2 adrenaline autoinjectors is recommended in patients with mast cell disorders and/or elevated levels of serum mast cell tryptase, and in patients with a history of very severe anaphylactic reactions who required the administration of multiple doses of adrenaline or who do not have rapid access to hospitals [28]. Based on currently available data [83], the expert panel considers basal tryptase levels above 7.95 µg/L as high in those patients with a history of anaphylactic reaction caused by hymenoptera sting with loss of consciousness and no cutaneous/mucosal involvement.

The expert panel also suggests prescribing 2 adrenaline devices to obese patients, as the injection might not reach the muscle and could therefore prove less effective.

Regarding LLRs, the risk of a systemic reaction is not currently considered so high as to require the prescription of adrenaline [74]. Nevertheless, Italian experts do not rule out the possibility of prescribing adrenaline to patients at risk of multiple stings (eg, beekeepers) and to those who had a single LLR, since in these patients the risk of a subsequent systemic reaction to a re-sting cannot be completely excluded compared with patients who have already experienced repeated LLRs [84,85].

European Medicines Agency Provisions on Adrenaline Autoinjectors

After evaluation of all available data, the European Medicines Agency (EMA) confirmed that intramuscular administration is the most indicated route for obtaining a rapid response in the treatment of anaphylaxis [86].

The EMA observed that correct administration of adrenaline by autoinjectors is affected by several factors such as needle length, thickness of subcutaneous fat, mode of operation of the autoinjector (whether spring-loaded and/or cartridge-based), angle with which it is placed into the skin, force used to activate it, and the patient's ability to follow the instructions properly.

Healthcare professionals are recommended to prescribe 2 autoinjectors, which patients should be advised to carry with them at all times, and to instruct the patient on how to use the autoinjector through educational material and practical training.

Diagnostic Criteria

Diagnosis is based on the classification of the type of reaction, confirmation of IgE-mediated pathogenesis, and identification of the stinging insect. On this basis, the clinical history and the results of in vivo and in vitro tests are crucial [3,87].

The history includes the description of the symptoms and of the course of the reaction (possibly documented by a medical report), the number of stings, the characteristics of the culprit insect (where possible), and the identification of specific risk factors for the severity of reaction [3].

It may be useful to show the patient an entomological notice board to facilitate the identification of the stinging insect; 73% of *Vespula*-allergic patients accurately identify this kind of hymenoptera on the board [88].

Since it is possible to document sensitization to venom in 10%-30% of patients with a negative history, only those with a history of previous systemic reaction [3,33,87,89] should be investigated. Table 6 shows the indications for performance of diagnostic tests.

Table 6. Indications for Performing Diagnostic Tests

Indicated
- In patients with a history of systemic reaction following hymenoptera stings
Not indicated:
- In persons with a positive family history for allergic reaction to hymenoptera stings
- In persons who have an unjustified fear of developing a systemic reaction to hymenoptera stings following news of fatal anaphylaxis in the media
- As screening in the general population
Optional:
- In patients with a history of large local reactions

In patients with a history of LLR, skin tests (as well as determination of specific IgE) may be considered optional, at the discretion of the clinician in specific cases, for example in patients at a greater risk of re-sting with recurrent and bothersome LLRs (eg, beekeepers, farmers), who could benefit from immunotherapy [90].

Skin tests are the gold standard for diagnosis and should be carried out at least 2 weeks after the last sting to exclude a false-negative response during the refractory period [3,33,87]. As this period may be even longer, tests yielding negative results in persons with a suggestive history should be repeated after 1-2 months. Conversely, in some patients, sensitization can only be demonstrated during the first week after the reaction [91].

European guidelines suggest performing skin tests gradually, that is, prick tests first, followed, if negative, by intradermal tests [3,33,87]. Intradermal tests should be performed even in cases of a positive prick test result in order to correctly identify a cutaneous endpoint for follow-up of VIT. Correct performance of skin tests with hymenoptera venom is of crucial importance, both to ensure an accurate diagnosis and to monitor VIT [92]. In particular, intradermal tests should be carried out with 0.02 mL of the allergenic extract injected into the dermis to generate a wheal of approximately 3 mm in diameter. The reading should be performed after 15-20 minutes; a positive result is defined as an increase of at least 3 mm in the average diameter of the initial wheal, with associated erythema. A morphological score should be used to enable comparison of the results. This consists of drawing, on transparent cellophane, the area injected and the area of the reaction after 15-20 minutes [93].

The prick test is carried out at 100 µg/mL. Intradermal testing can start from very low concentrations, according to the symptoms presented by the patient; concentrations ranging from 0.001 to 1 µg/mL are normally used.

The sensitivity of the prick test is lower than that of the intradermal test. In a study performed on 301 patients allergic to *Vespula* species venom, prick testing identified 49% of cases, while the combination of prick and intradermal reaction facilitated a diagnosis in 94% of cases [94]. Intradermal testing with nondialysate venoms can be irritating at concentrations higher than 1 µg/mL [95]. In Europe, standardized venoms of *A mellifera*, *Vespula* species, *Polistes* species, and *V crabro* are currently available; the venoms of *Vespula* and *Polistes* consist of a mix of clinically relevant species (*Vespula* species: *V vulgaris, V flavopilosa, V germanica, V maculifrons, V pennsylvania*, and *V squamosa*; *Polistes* species [American]: *P annularis, P exclamans, P fuscatus*, and *P metricus*). Because of low cross-reactivity between European and American *P venoms* [96], extracts of *P dominula* are now available for both diagnosis and VIT [97]. On the other hand, high cross-reactivity between *Vespula* species venom and *V crabro* has been confirmed [98]. A recent study [99] suggested that, in patients with a proven reaction to *V crabro*, VIT with *V crabro* venom may have a higher safety profile.

Skin tests with venoms are generally safe, even in patients with mastocytosis [100,101]. One study highlighted safety, even if the tests are carried out simultaneously at different concentrations [102]. The Italian expert panel considered that available data are insufficient and recommended a preliminary step where the same concentration of several venoms is simultaneously used for skin testing. A higher concentration should only be used after reading the reactions to the first set. This caution is to be maintained, especially in patients with severe anaphylactic reaction or mast cell disorders.

The total IgE dosage may help to ensure correct interpretation of specific IgE values, especially if they are very low [103]. In the event of very high levels, the presence of concomitant pollinosis should be investigated.

Serum specific IgE can be detected immediately after the sting, even if the best period for its determination is 1-4 weeks after the sting [3].

The sensitivity of serological tests using whole extracts is generally lower than that of skin tests. In general, in vitro tests for determination of specific IgE to the whole venom extract can be negative in up to 20% of patients with positive skin test results, whereas approximately 10% of patients with negative skin test results are positive in the in vitro test. Therefore, guidelines suggest performing both tests [3,33,87,104].

The sensitivity of serological tests for *Vespula* species is lower than that of tests for bee venom: 98% to 100% for bee [105,106] and 83% to 97% for *Vespula* [105,106]. A new in vitro method enriched with the recombinant allergen Ves v proved more sensitive than traditional methods [94]. Furthermore, it has recently been hypothesized that negative skin test results with *A mellifera* extract may be due to a minor presence or even absence of some allergens in diagnostic and therapeutic extracts [107]. It is to be noted that the values of serum specific IgE to *V crabro* venom may vary according to the laboratory method used.

Diagnosis is complicated by sensitization to multiple venoms in patients who have not identified the stinging hymenopteran. The double positivity to venom of *A mellifera* and *Vespula* species is found in 25%-40% of cases and may be due to double sensitization, cross-reactivity between epitopes present in both venoms (hyaluronidase; Api m 5 and Ves v 3; Api m 12 and Ves v 6), and cross-reactive carbohydrate determinants (CCDs). The commercial availability of some major allergens expressed in recombinant form enables implementation of component-resolved diagnosis (CRD) [103,108].

Bee venom–allergic patients often have a broad sensitization profile. Api m 1, the most relevant allergen of bee venom, is not sensitizing in up to 43% of cases [109]. The combination of 2 allergens (Api m 1 and 10) enables diagnosis in 86.8% of cases; the combination of 6 allergens (Api m 1- 5, Api m 10) has a sensitivity of 94.4% [109]. Currently marketed recombinant allergens include rApi m 1, rApi m 2, rApi m 3, rApi m 5, and rApi m 10. Patients with allergy to *Vespula* venom are sensitized mainly to Ves v 1 and Ves v 5. The combined search of specific IgE toward these 2 recombinant allergens enables the identification of 92%-94% of *Vespula*-allergic patients [110,111].

In Southern Europe, double *Vespula-Polistes* sensitization is more frequent than Apis-*Vespula* sensitization [112], and cross-reactivity between allergens of 2 species often poses diagnostic difficulties [113,114]. In cases of difficult interpretation between sensitization *Vespula* and sensitization to *Polistes*, the use of Ves v 5 and Pol d 5 seems to be

helpful in clinical practice, provided that the difference in specific IgE levels between the 2 molecules is particularly significant, with at least double values of one recombinant over the other [114-116]. Furthermore, where available, phospholipases (Pol d 1/Ves v 1) have proved useful in identifying the probable sensitizing species in *Vespula*/*Polistes*–sensitized patients [114]. A new major allergen of the venom of *P dominulus*, Pol d 3 (dipeptidyl peptidase IV) has recently been identified, although it was found to be cross-reactive with both *Apis* and *Vespula* venoms [117].

IgE to CCDs can explain multiple positive in vitro results; serum determination of CCDs (bromelain or MUXF3) allows for greater diagnostic accuracy [105]. *Polistes* venom is CCD-free and is therefore not affected by this cross-reactivity [118].

Figures 1 and 2 show the diagnostic algorithm for cases of double-positive results with *Apis*-*Vespula* and *Vespula*-*Polistes*.

In summary, CRD can be used to discriminate between primary sensitization and cross-reactivity in patients with double-positive results in diagnostic tests with whole extracts, thus enabling the specialist to choose the most suitable venom for VIT and to avoid treatment with double VIT. However, the decision should rely not only on CRD results, but should also take into account the severity of the reaction and the patient's general health status. CRD may also help in the diagnosis of patients with a history of systemic reaction and negative results in standard diagnostic tests [119,120].

CAP-inhibition also makes is possible to distinguish between double sensitization and cross-reactivity, although it may be relatively expensive and its results could prove difficult to interpret [103]. It appears to be very useful in cases of double *Vespula-Polistes* cosensitization, when CRD cannot discriminate between different possibilities [114,115].

The basophil activation test (BAT) is the most widely used blood cell–based diagnostic test in Europe in selected situations. If performed in highly specialized laboratories, it can identify approximately two-thirds of patients with a positive history and negative skin and serological test results [121]. BAT is also recommended in patients with double-positive results and inconclusive in vivo or in vitro test results with recombinant allergens [119]. Since BAT results are influenced by the presence of venom CCDs, using CCD-free recombinant allergens ensures greater diagnostic accuracy [119,122]. The role of BAT as a diagnostic tool in patients with mast cell disorders and negative venom-specific IgE and skin test results remains controversial [123-126].

Sting challenge with a live insect should not be used for diagnostic purposes owing to the risk of potentially severe systemic reactions and its low negative predictive value [127].

In the presence of systemic reactions, basal serum tryptase levels should always be determined, as adults affected by mast cell disorders and/or elevated basal tryptase levels have a significantly greater risk of severe reactions to hymenoptera stings [16,128].

Moreover, patients should be investigated for mastocytosis, even in the absence of cutaneous manifestations compatible with mast cell disorders and increased tryptase levels, and in cases of severe anaphylactic reaction with syncope without urticaria and/or angioedema and a REMA score ≥2 [129]. High basal serum tryptase is not pathognomonic of mastocytosis and can also be found in hematological diseases (especially those of the myeloid lineage), end-stage chronic renal failure,

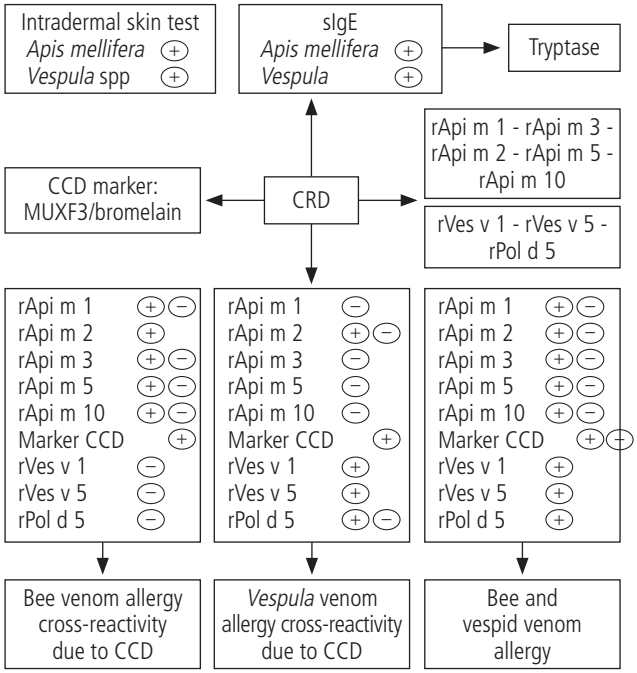

Figure 1. Diagnostic algorithm in honeybee and vespid venom allergy. CRD indicates component-resolved diagnosis; CCD, cross-reactive carbohydrate determinant.

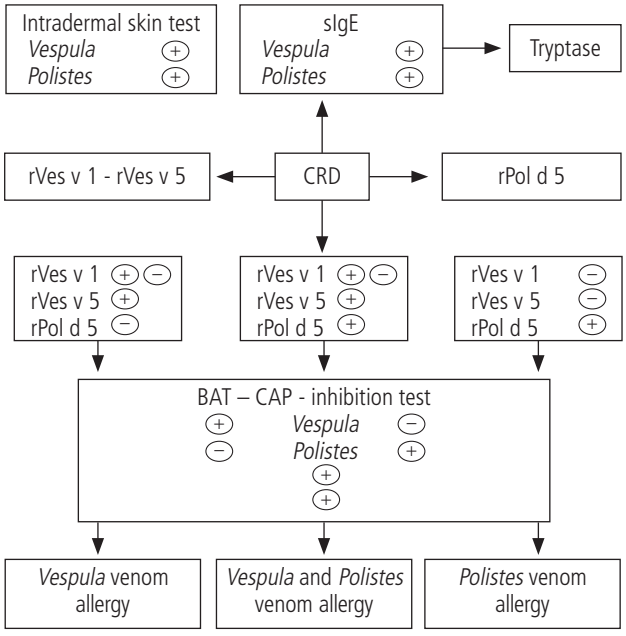

Figure 2. Diagnostic algorithm in *Vespula* species and *Polistes dominula* venom allergy. CRD indicates component-resolved diagnosis; BAT, basophil activation test.

Table 7. Allergological Diagnosis in Hymenoptera Venom Allergy: Practical Considerations

- Skin tests represent the diagnostic gold standard and should be performed at least 2 weeks after the sting; if negative, they should be repeated after 1-2 months.
- Prick tests, even if positive, should be integrated with intradermal tests.
- Simultaneous testing of the same concentration of more venoms is to be preferred. The next concentration should only be tested afterwards.
- Skin tests with venoms are generally safe, even in patients with mastocytosis, if performed by trained personnel in a suitable environment.
- Validated methods are to be used for the determination of serum specific IgE to venom allergens.
- There is no correlation between the severity of a reaction and the scores of in vivo and in vitro diagnostic tests.
- The use of component-resolved diagnosis (CRD) is indicated in cases of polysensitization or negative allergy tests in patients with a proven history of previous systemic reaction.
- At present, CRD makes it possible to distinguish between allergy to *Apis mellifera* and allergy to Vespula species venoms; the value of CRD is limited in cases of double positivity to *Vespula-Polistes.*
- The CAP-inhibition method is appropriate in cases of double positivity to *Vespula-Polistes*, when CRD is not valid.
- The basophil activation test should be carried out in highly specialized laboratories for diagnostic purposes, only in specific situations. Its role as a diagnostic tool in patients with mast cell disorders and negative venom-specific IgE and skin test results remains controversial.
- When a severe systemic reaction occurs, baseline serum tryptase levels should be measured.

onchocercosis in treatment, and abdominal aortic aneurysm (2 cases with anaphylaxis to hymenoptera venom were reported) [130].

Table 7 shows practical considerations in the diagnostic flow chart for hymenoptera venom allergies.

Pediatric Aspects

Diagnostic tools are no different from those used in adults. Furthermore, in children, the degree of skin sensitization does not correlate with the severity of the reaction [131].

Specific Immunotherapy

Definition and Mechanisms of Action

VIT is the therapy of choice for patients who develop a systemic reaction after hymenoptera sting, since it can induce tolerance to venom [33,73,132-134].

VIT consists of an induction phase and a maintenance phase. The induction phase involves subcutaneous administration of increasing doses of the venom extract up to the protective dose, ie, 100 μg. Protocols used for this purpose differ in length. The maintenance phase involves the administration of fixed amounts of venom at regular time intervals to maintain tolerance.

The mechanisms of action of immunotherapy are numerous and impact at both early and late stages. They include an increase in specific IgG1 and IgG4 levels [135-138], a cytokine shift characterized by reduction in IL-4 and IL-5 and an increase in IFNγ [139-141], the reduced expression of adhesion molecules [142], lymphocyte downregulation [143], reduction of mast cell and basophil activation [144,145], immunomodulation by IL-10 [137,146-148], and induction of regulatory T cells [131,149,150].

Indications

VIT is indicated in the following circumstances: (*a*) children and adults with a systemic reaction involving organs other than the skin [90]; (*b*) systemic skin reactions in cases of high risk of exposure and/or impaired quality of life [151] in adults [90]; (*c*) patients with clonal mast cell disorder and a history of a systemic reaction [152], even though sensitization can be weak or sometimes transitory.

Information on children with cutaneous-mucosal reactions is provided in the appropriate section.

VIT is not generally indicated in cases of LLR, as the risk of progression in systemic reactions is low (2%-7%) [89,153,154], especially if the LLRs are recurrent [84,89]. The clinical efficacy of VIT can be seen in the fact that it reduces the extent of consecutive LLRs [155,156]. Its use is not contraindicated in patients with recurrent and severe LLRs. VIT is not indicated unusual reactions (ie, serum sickness–like manifestations, central nervous system manifestations, and hematological, muscle, and renal reactions), where the mechanism of action is unclear [73].

Clinical Efficacy

Specific subcutaneous immunotherapy for hymenoptera venom is the only treatment able to protect patients from systemic reactions after subsequent stings [90]. Numerous studies have evaluated the efficacy of VIT, both with sting challenge and field sting. In a recent Cochrane Review, the percentage of nonprotection was 2.7% in treated patients compared with 39.8% in patients not undergoing immunotherapy [156]. Regarding vespid venom, protection is between 91% and 96%, while for bee venom it ranges between 77% and 84% [14,90,157-167]. Studies performed on European populations, including Italian cases, show that about 70% of treated patients are allergic to vespids [164,166].

The different methods of preparation of the extracts do not affect their protective capacity; the efficacy of purified aqueous and aluminum hydroxide–adsorbed preparations (the so-called depot preparations) is in fact comparable [168].

As for VIT with *Polistes* venom, the use of *P dominula* venom to treat European patients should be preferred, since American *Polistes* venom extracts have been reported to lack a protective effect [6,169]. However, a recent study [170], in which incomplete in vitro cross-reactivity was confirmed, did not detect differences in clinical protection between VIT with a mixture of American *Polistes*

and VIT with *P dominula* after field sting. Further studies are necessary to confirm these data.

Table 8 describes known risk factors for reduced efficacy of VIT.

Protocols

Over the years, various induction protocols have been proposed with the aim of reducing the incidence of adverse effects while rapidly achieving clinical protection and favoring adherence. According to the chosen protocol, the maintenance dose may be reached in a few weeks, a few days, or a few hours [33,73,171]. Conventional and "clustered" protocols do not significantly differ from one another as far as safety is concerned [172]. Ultrarush induction protocols have proved effective [173-175], inducing early changes in immunological parameters associated with the efficacy of VIT (IgE, IgG4) [176]. To increase adherence to VIT, management of immunotherapy protocols can be flexible, for example, by switching from an aqueous extract to a depot extract by the same manufacturer, with no impact on efficacy or safety [177].

The starting dose of VIT is between 0.001 μg and 0.1 μg; however, treatment can be initiated safely from 1-5 μg of venom using a rush protocol both in adults and in children [172, 178]. The maintenance dose of 100 μg is considered the gold standard in both adults and children and must be increased to 200 μg [179] in unprotected patients (usually adults) and, according to some authors, in beekeepers [13]. Once the maintenance dose has been reached, the intervals between doses should be maintained at 4 weeks in the first year and gradually increased to 6-8 weeks in subsequent years, with no reduction in the clinical efficacy of VIT [180]. According to some authors [181-183], after the third year of VIT, the interval can be progressively lengthened up to 12 weeks. Other studies evaluated 6-month intervals; this extension is not currently recommended because it could affect the effectiveness of the treatment [182].

Pharmacovigilance data from the European Medicines Agency indicate that there are no reports of toxic effects of aluminum hydroxide in products for allergen immunotherapy. In VIT with a maintenance dose of 200 μg and in VIT with 2 different venoms, it is preferable to use an aqueous extract for at least 1 of the 2 VITs as a precautionary measure [90]. A recent paper analyzed the aluminum concentration in urine and blood in 2 groups of patients: those never treated with aluminum-depot subcutaneous immunotherapy and those treated with aluminum depot VIT. No differences were detected in urine aluminum concentrations between the 2 groups; the same was true of blood using free-gel monovette. However, given the small amount of the free-gel detections, data from blood remain inconclusive [184].

Currently, there are no guidelines in the literature on the management of product deficiency during maintenance, which was reported in 2016 owing to the sudden unavailability of some extracts. A recent multicenter study prospectively collected data on switching VIT and reported that switching VIT from one manufacturer to another is a safe option, if necessary, in patients who had previously tolerated VIT, even without reducing the previous maintenance dose, in a proper medical setting staffed by experienced personnel [185,186]. In patients who experienced previous severe systemic reactions during VIT, the treatment should be restarted with a rush/ultrarush protocol in centers experienced in hymenoptera venom allergy and VIT or with a conventional protocol in less experienced centers.

Duration

In patients with no specific risk factors, VIT should be continued for 5 years [187]. Based on current literature, the

Table 8. Risk Factors for Reduced Effectiveness of Venom Immunotherapy (VIT)

Risk Factor	Notes
Age	Adults are at higher risk than children, as patients under the age of 16 generally have a more favorable prognosis. VIT is not recommended for cutaneous/mucosal systemic reactions in patients under the age of 16, except in cases of high risk of exposure or impaired quality of life [50,152,235,270].
Bee venom	The protection rate for bee venom is lower than for vespid venom [28,73,160,189,191,271]. The reason for this discrepancy is not yet fully understood. Recent studies of molecular allergy have shown that relevant allergens to bee venom may be poorly represented in some extracts used for specific immunotherapy [107,272].
Severity of onset	Patients with severe systemic reactions to hymenoptera sting are less likely to have long-term protection (based on the number and frequency of stings received after suspension of immunotherapy) compared with patients who experience milder reactions [159,188,189,241,271,273].
Systemic reactions during VIT	Patients with adverse reactions to VIT are at greater risk of incomplete protection than patients who tolerate VIT [166,191,271].
High tryptase values and clonal mast cell diseases	In some studies, clonal mast cell diseases are correlated with lower clinical efficacy [207,274]. However, other studies do not support this conclusion and confirm a protection rate of 67%-85% [100,152,255,256,275]. In a recent prospective study, protection was 86% after field sting in patients with clonal mast cell disorders [256]. Overall, VIT should be considered an effective and safe option in these patients.
Angiotensin-converting enzyme inhibitors	A single study on 1532 patients reported that this category of drugs could be a risk factor for reduced clinical efficacy, as demonstrated by sting challenge [166].

recommended duration of VIT is 3-5 years in adults and children [73,90,187]. One year of VIT did not provide sufficient protection in about a quarter of treated patients [188].

After 3 years of VIT, 83% to 100% of patients remain protected against subsequent stings for a further 1 to 3 years [158,159,188,189-193].

A VIT schedule equal to or longer than 5 years provides more prolonged efficacy after the interruption [189,194,195]. At present, there are no data on the maintenance of protection for periods longer than 15 years, especially in the case of VIT with bee venom. Table 9 shows the risk factors for relapse after interruption of VIT.

When skin and serological tests yield negative results, VIT can be safely interrupted. However, this rarely occurs [73]. After 5 years of VIT, there is an average reduction in specific IgE of 58%-70% overall compared with baseline and a lower reduction in older patients or in patients with very severe reactions. This reduction is not correlated with lower clinical efficacy [196]. Indeed, the decision to stop VIT cannot be based solely on the reduction in specific serum IgE levels, since stung and protected patients during VIT have higher IgE levels at the end of the 5-year treatment than patients who have not been stung, although they are clinically protected [196]. It was recently shown that an increase in the IgG/IgE ratio correlates with a reduction in the frequency of specific IgE and skin reactions in patients who have undergone at least 3 years of VIT [197]. However, no validated tests are currently able to predict venom tolerance owing to variability in immunological parameters during VIT [198].

In clinical practice, the patient is rarely stung during VIT, as he/she takes environmental prophylactic measures. It therefore becomes difficult to decide whether or not to suspend VIT in the absence of proof of field protection. Even though the sting challenge test is still the most reliable method and the gold standard for monitoring the effectiveness of VIT [90], it cannot be performed to demonstrate the effectiveness of VIT in some countries for ethical and management reasons [199]. A recently developed microsyringe challenge method [200] has yet to be validated.

Proper management of patients requires a full knowledge of the risk factors that could negatively impact on the protection provided by VIT. According to prevalent expert opinion, patients with mast cell disease should receive lifelong treatment [201,202]. However, this suggestion is not confirmed by controlled studies [90]. A recent study in a selected population indicated that mastocytosis should be considered in patients who experience severe reactions at re-sting after discontinuation of VIT. On this basis, patients with mastocytosis and hymenoptera venom allergy should receive lifelong VIT [203].

The decision to prolong VIT over 5 years should be shared with patients based on specific risk factors and impact on quality of life; there is currently no contraindication to continuing VIT for more than 5 years.

Patients should always be followed up over time; this aspect is not properly addressed in European and American guidelines. Based on current knowledge, the present panel of experts suggests the following:

– Patients not undergoing VIT but equipped with an adrenaline autoinjector because of a previous systemic reaction should attend a follow-up visit in case of re-sting and have their history updated at each re-order of adrenaline, including refresher training on device use. In the absence of re-sting, it is useful to schedule a follow-up visit every 2 years, in order to perform skin and/or serological allergy tests before further prescription of adrenaline.

Table 9. Conditions for High Risk of Relapse After Discontinuation of VIT

Risk Factor	Notes
Adult population compared with pediatric patients	[73]
Severe pre-VIT systemic reaction	Based on data from 4 prospective studies recruiting 386 patients with severe reactions at re-sting, 4.1% had mild and 14.5% had severe pretreatment reactions [187].
Allergy to bee venom	The risk of systemic reactions after discontinuation of VIT for bee was 16% vs 8% of patients treated with wasp venom [189].The reasons, which are not entirely known, are partly related to the amount of venom delivered with sting and to the amount of venom administered in VIT. It has also been hypothesized that some major bee allergens may be missed or underrepresented in extracts used for VIT [109].
Systemic reaction caused by VIT	Patients who developed systemic reactions to VIT had a 38% risk of re-sensitization compared with those who tolerated treatment (7%) [276].
Failure to achieve protection during VIT	[192]
Clonal mast cell diseases and elevated baseline tryptase levels	Please refer to the mastocytosis section.
Repeated stings	According to European studies, patients repeatedly stung after discontinuation of VIT have a greater risk of systemic reactions that may become progressively more severe [189]. Professionals who are particularly at risk include beekeepers and gardeners, who need treatment for an indefinite period.
Persistence of high scores in diagnostic tests after 5 years of VIT	[241]

Abbreviation: VIT, venom immunotherapy.

– Patients undergoing VIT should undergo monitoring of skin reaction and/or determination of specific IgE at 3 and 5 years or in the case of a systemic reaction to a field sting.
– Patients at risk of multiple stings or with risk factors for relapse after interruption of VIT should attend a follow-up visit in case of re-sting and have their clinical history updated at each re-order of adrenaline, including refresher training on device use.

Adverse Reactions

The literature reveals considerable variation in the incidence of adverse effects due to VIT (0%-46%) [204,205]. This is likely due to multiple factors, including different classification systems for severity, differences in the quality of extracts (nonpurified, aqueous, and depot extracts), and differences in administration protocols.

A recent systematic review of the literature [90] examined 11 observational studies: VIT was associated with a 14.2% risk of adverse events in patients treated with bee venom and a 2.8% risk in those treated with vespid venom. Another systematic review [206] reported a mean frequency of 28.9% for adverse events with bee venom, of which 50.4% were systemic reactions and 10% local extended reactions.

Large-scale studies showed that most reactions to VIT occurred in the build-up phase, including systemic reactions (up to 20% [1.9% during the build-up phase, 0.5% during maintenance from a total of 26 601 injections]), of which 8.4% were moderate to severe [204].

LLRs to VIT are frequent, especially in the build-up phase; they do not represent a risk factor for subsequent systemic reactions, do not require dose reduction, and do not prevent the protective dose from being reached. In the case of systemic reactions, it is preferable to reduce the dosage in the build-up phase (eg, by stepping down 1 or 2 doses) and continue with the last well-tolerated dose [90].

The risk factors for systemic reactions during VIT are bee venom, high basal tryptase values in patients allergic to wasps, mast cell clonal diseases, and rush and ultrarush protocols [73,204,207,208].

However, some authors do not consider rush or ultrarush induction protocols to be dangerous, since they were able to demonstrate a low risk of systemic reactions and a safety profile equivalent to or even better than slower protocols [163,209-211].

Local adverse reactions are less frequent with depot extracts than with aqueous extracts [212,213]. A systematic review confirmed that the incidence of systemic reactions is significantly higher for bee venom than for vespid venom (25.1% vs 5.8%), while no differences were found between aqueous and depot extracts in treated patients [214]. However, this review did not compare nonpurified aqueous extracts with purified aqueous extracts. In fact, the use of purified aqueous extracts seems to correlate not only with a lower frequency of major local reactions, but also with a lower frequency of systemic reactions than nonpurified extracts [215,216].

Results from double-blind, placebo-controlled studies show that premedication with antihistamines improves tolerance to VIT while maintaining efficacy [217-220]. On this basis, recent EAACI guidelines [90] recommend antihistamines, which can prevent extensive local reactions and mild systemic reactions. The possibility of masking warning signs and symptoms of more severe reactions, especially if rapid protocols are used, led the Italian expert panel to indicate this treatment as optional.

Off-label premedication with omalizumab can be successfully implemented in patients who experience systemic reactions to VIT and when premedication with antihistamines is insufficient [221,222].

VIT and Pregnancy

Studies on the safety of VIT in pregnancy are limited [223,224], mainly for ethical reasons. One of the potential risks of immunotherapy, in addition to the management of possible adverse reactions, could be the induction of a T_H2-T_H1 cytokine shift that acts against the overall T_H2 profile of pregnancy and has been claimed to prevent fetal rejection [225]. In a 1990 study of 26 patients with multiple pregnancies undergoing VIT, the authors estimated a 3%-5% risk of field sting anaphylaxis in women not undergoing VIT during pregnancy, while the risk of anaphylactic reaction during VIT was 1% in the maintenance phase and 5% in the build-up phase. In addition, anaphylaxis has potentially severe consequences for the fetus. The risk of maternal-fetal complications in pregnant women undergoing VIT was similar to that of women not undergoing VIT [224].

In a 2002, Markert et al [226] reported a case of preterm delivery due to placental abruption at week 24 in a woman who had started the build-up phase of immunotherapy during the first weeks of gestation. VIT was continued at the maintenance dose of 50 µg. Analysis of the placenta demonstrated a T_H1 pattern with infiltrated cytotoxic T lymphocytes [226]. In contrast, a more recent case report of in vitro fertilization considered VIT to be safe [227].

In conclusion, as confirmed by recent European guidelines [228], immunotherapy should not be started during pregnancy. However, given the low risk of adverse effects, VIT should not be interrupted during pregnancy if the patient is already taking and tolerating VIT [204].

Adherence to VIT

Adherence to specific immunotherapy is key to successful management of patients with respiratory allergies [229]. In the case of VIT, a recent Italian study showed high percentages of adherence at 3 years (95%) and 5 years (84%) of treatment [230].

Pediatric Aspects

Although the efficacy of VIT is known in children, there are no double blind, placebo-controlled trials in pediatric patients [231]. Treatment is recommended in children who experience systemic reactions with cardiovascular and/or respiratory involvement after hymenoptera stings [73,231].

In children who only experience cutaneous systemic reactions, VIT is not routinely performed [90,232,233], since a long-term prospective study has shown that children with this type of reaction have a 10% risk of systemic reaction [131]. However, there may be particular situations of increased risk of re-sting (eg, children of beekeepers), possibly associated with

concern on the part of parents and children, distance from an emergency department, and unavailability of school staff who know how to administer antiallergic drugs. These conditions also highlight the need for VIT in cases of children affected only by urticaria [73].

As far as the risk of systemic reactions with respiratory or cardiovascular involvement is concerned, an observational study of pediatric patients followed for 15-20 years showed that the risk of recurrence of anaphylaxis in untreated children was 32%, compared with 1%-3% in those treated with VIT [154]. In a recent 6-year follow-up European pediatric study, 62% of children allergic to venom and not treated with VIT tolerated subsequent stings, whereas 18% had severe systemic reactions [234]. The proportion of therapeutic failure of VIT is lower in children than in adults (about 2% of treatments) [49,189,235].

Induction patterns in children are similar to those used in adults [131]. Regarding accelerated protocols, a pediatric study [236] of 43 children and adolescents (aged 4 to 18 years, with a 1-4 Mueller grade systemic reaction after bee or wasp sting) undergoing ultrarush VIT found no systemic reactions. A recent study of pediatric and adult patients confirmed the tolerability of the rush schedule in children [237]. Another study compared the safety of 3-day rush induction protocols

Table 10. Pediatric Aspects of Hymenoptera Venom Allergy

Epidemiology	Hymenoptera venom allergy is the second cause of severe reactions in children (20.2%), after food allergy [19]. Prevalence: asymptomatic sensitization, 3.7% [42]; large local reactions, between 0.9% [43] and 20.8% [44]; systemic reactions, <1% [15,42]. Risk factors for systemic reactions [45,46]: bronchial asthma, atopy (according to some studies) Clinical: the cutaneous and cardiocirculatory systems are the most affected; skin symptoms are the only clinical manifestation in 60% of cases [47]. Prognosis: favorable regarding re-sting in studies with sting challenge [48] and field sting [49,50].
Diagnosis	– Diagnosis is no different from that of adults – The degree of skin sensitization does not correlate with the severity of the reaction [131].
Specific immunotherapy (VIT)	Indications: – Children who develop a systemic reaction with cardiovascular and/or respiratory involvement [73,232]. – VIT is usually not administered in children with only cutaneous systemic reactions [90,233] owing to the very low risk of developing a more severe systemic reaction. – Children with an increased risk of exposure (eg, children of beekeepers) and/or children or their parents who show anxiety, are living far from emergency departments, or attending school not staffed with personnel trained to administer antiallergic drugs may also undergo VIT in cases of skin reactions only [73]. Risk of anaphylaxis at re-sting: – Children not undergoing VIT: 32% vs 1%-3% of patients treated with VIT [154]. – Recent European study with 6-year follow-up: 18% of non–VIT-treated patients (while 62% tolerated subsequent stings) [233]. Efficacy: – The percentage of failure of VIT in children is lower than that of adults (about 2%) [49,189,235]. – The prognosis after discontinuation of VIT is better than that of adults: only 5% of children with a severe pretreatment reaction develop nonsevere systemic reactions at re-sting [149], compared with 16% of adults [241]. Induction schemes: – As in adults [131]. – Accelerated (rush, ultrarush) and clustered protocols are well tolerated by children [236-240] – As in adults, avoid excessively rapid patterns with bee venom – As in adults, the maintenance dose is 100 μg, to be increased to 200 μg in unprotected patients Duration: – The panel of experts suggests at least 5 years of VIT in pediatric patients – Proper follow-up and appropriate educational programs are necessary.
Quality of Life	– Allergy to hymenoptera venom in children can have a negative impact on the quality of life of their parents. – There are specific questionnaires on the quality of life of pediatric patients allergic to hymenoptera venom and their parents [269].
Use of adrenaline	Dose: intramuscular adrenaline in the vastus lateralis muscle at 0.01 mg/kg (maximum dosage 0.3 mg) Autoinjector: – The fixed dosage involves a risk of administering a higher or lower dose of adrenaline; for children weighing between 15 and 30 kg with severe anaphylactic reaction or concomitant bronchial asthma, it is advisable to use the adult dosage. – It should be prescribed to children with systemic reactions (not just cutaneous reactions), with a high risk of exposure, risk factors for lacking clinical protection, elevated baseline mast cell tryptase levels, or mast cell disorders [28,33,70,71].

with conventional 4-month regimens [238]: no differences were found between the protocols in terms of systemic reactions (19% and 23.2% with rush and conventional protocols, respectively). In a 2016 study [239], the ultrarush induction protocol of Birnbaum et al [240] (101 µg cumulative in 210 minutes) was compared in adults and children (systemic reactions in 7.7% of adults vs 3.7% of children). It is important to remember that, as in adults, excessively rapid schedules should be avoided when using bee venom [237].

Children have a better prognosis than adults with regard to the maintenance of efficacy upon discontinuation. Golden et al [154] followed patients for 20 years and found that nonsystemic reaction recurred at re-sting in only 5% of children with a severe pretreatment reaction, compared with 16% of adults [241].

Among 40 children who received VIT for a mean of 3 years, 50% developed a new anaphylactic reaction after a median follow-up of 13 years; of note, 95% had not received adequate follow-up after discontinuation of VIT [242].

In view of these data, the panel of experts suggests that VIT should last for at least 5 years in pediatric patients. Moreover, children should also undergo periodic check-ups, and suitable educational programs are necessary.

Table 10 summarizes the pediatric aspects of hymenoptera venom allergy.

Management of the Patient With Concomitant Diseases

Heart Disease

The presence of cardiovascular disease is a major risk factor in hymenoptera venom–allergic patients owing to the severity of anaphylaxis after a sting. In fact, increased mast cell density has been identified in arterial intima and adventitia in ischemic heart disease, aortic valve stenosis, and hypertrophic cardiomyopathy [243]. Furthermore, mast cells in ischemic myocardium are richer in histamine and tryptase than mast cells in healthy myocardium.

Venom components can induce the release of serotonin and adrenaline, which increase platelet aggregation, thus increasing the likelihood of thrombosis resulting from an increase in factor V and the release of a thromboplastin-like substance from the vessel wall. These and other substances released by mast cells could have a negative inotropic and chronotropic effect. During the anaphylactic reaction, de novo synthesis of LTC4 and PGD2 at the level of the heart may result in vasoconstriction. Similarly, in some patients with coronary artery disease, stimulation of H_1 receptors may cause vasoconstriction of large-caliber coronary arteries, in contrast to patients with a healthy myocardium [244]. Activation of metalloproteinase also degrades the connective tissue of atheromatous plaques, thus increasing the risk of ischemia.

Physiologically, the decrease in blood pressure that occurs in the anaphylactic reaction leads to reduced perfusion in the sinuses of Valsalva and to coronary hypoperfusion.

Kounis syndrome [245], also known as cardiac anaphylaxis, is characterized by signs and symptoms that are similar to those of coronary syndrome. This condition may be due to the direct action of the venom on the coronary endothelium or to degranulation of mast cells due to the allergic reaction, with direct release of inflammatory mediators into the coronary vascular system (histamine, kinase, tryptase) and synthesis of leukotrienes, which act as powerful vasoconstrictors of the coronary arteries [246].

In patients allergic to hymenoptera venom, in whom a subsequent allergic reaction may be more severe or even fatal, VIT is elective, even if the patient has had a myocardial infarction or severe ventricular arrhythmia. In these patients, VIT was found to be associated with a low incidence of systemic reactions and with a certain degree of efficacy [247].

The patient with heart disease is often treated with ß-blockers and angiotensin-converting enzyme (ACE) inhibitors, which are commonly prescribed for hypertension and heart failure. ß-Blockers can reduce the efficacy of adrenaline administered to treat systemic reactions to hymenoptera venom. However, their use is not contraindicated during VIT [228]. Indeed, a recent report indicated that β-blockers had no significant clinical effects with respect to the need for adrenaline dosing in patients with anaphylaxis seen in the emergency department [248].

Suspension of ß-blockers, which is limited to the rush or ultrarush induction phase of VIT, should be discussed with cardiologists. ACE inhibitors can increase the severity of the reaction in patients not treated with VIT, although they do not seem to increase the risk of systemic reactions during VIT. According to a recent study [166], ACE inhibitors constitute a risk for reduced protection of VIT to insect challenge. Therefore, their suspension remains at the discretion of the clinician based on the risk-benefit ratio [16].

Before starting VIT, cardiovascular disease, its pharmacological treatment, and the risk of anaphylaxis with consequent administration of adrenaline should be carefully evaluated on an individual basis, preferably together with the consulting cardiologist (strength of recommendation, D).

Elderly Patients

According to the guidelines of EAACI and the American Academy of Allergy, Asthma and Immunology (AAAAI), VIT should be taken into consideration in older adults, even if they have experienced a nonsevere systemic reaction, provided that they have risk factors such as concomitant vascular diseases, treatment with ACE inhibitors and/or ß-blockers, severe chronic obstructive pulmonary disease, and reduced quality of life due to the previous anaphylactic event [73,87].

No increased risk of adverse effects or an increase in emergency treatments of elderly patients has been demonstrated to date (strength of recommendation, D).

Malignancy

Malignant neoplasms are considered absolute contraindications for specific immunotherapy with aeroallergens, although not all guidelines agree. This contraindication has been established for safety and ethical reasons [249], since the risk of an exacerbation of neoplastic disease by allergen immunotherapy is only theoretical, although a possible immunological interaction between neoplasm, cancer treatments, and allergen

immunotherapy cannot be completely excluded. However, in patients allergic to hymenoptera venom with a high risk of severe reactions to subsequent stings (eg, previous life-threatening reaction or clonal mast cell diseases), VIT appears to prevent fatal events even in the presence of cancer [228,250] (strength of recommendation, D).

Autoimmune Diseases and Immunodeficiency

Some guidelines consider multiorgan autoimmune diseases in remission to be relative contraindications for immunotherapy. If autoimmune diseases are clinically active, the contraindication is absolute [228] (strength of recommendation, D).

VIT is not contraindicated in patients with organ-specific autoimmune diseases (eg, diabetes mellitus, Hashimoto thyroiditis, Crohn disease, ulcerative colitis, rheumatoid arthritis), provided the disease is stabilized before starting treatment [251] (strength of recommendation, D).

Immunodeficiency has a different impact and a different pathophysiological mechanism. According to some guidelines, concomitant treatment with immunosuppressive drugs means that allergen immunotherapy is contraindicated, since they could have a negative impact on the effectiveness of VIT. HIV infection, in particular, is a relative contraindication to VIT that can be assessed on an individual basis (strength of recommendation, D). AIDS with a confirmed category C disease (1993 Revised Classification, Centers for Disease Control) is an absolute contraindication to VIT [228] (strength of recommendation, NR).

Mastocytosis

Anaphylaxis is the most severe clinical manifestation of systemic mastocytosis, and hymenoptera stings are reported to be the most frequent cause (19%-53% of cases) [252].

The preferential association between mastocytosis and allergy to hymenoptera venom is well known and widely studied [100]. The prevalence of hymenoptera venom allergy in the European adult population is between 0.3% and 8.9% and rises to 20%-30% in patients with mast cell disorders [3,252,152]. On the other hand, the prevalence of systemic mastocytosis in the general population is 1-1.3 cases per 10 000, which increases significantly in patients with hymenoptera venom allergy (5%-8%) [25,252].

Patients with systemic mastocytosis without skin involvement presenting hymenoptera venom anaphylaxis probably represent a specific phenotype characterized by an excellent prognosis, male predominance, lower values of serum tryptase, and lower proportions of bone marrow mast cells than in indolent forms. Moreover, this phenotype does not include other symptoms due to mediator release and affects no myeloid lineages other than mast cells [253]. In contrast, hymenoptera anaphylaxis appears to be absent in patients with aggressive forms of systemic mastocytosis, despite the greater mast cell burden [254]. In patients with onset of mastocytosis after hymenoptera anaphylaxis, progression to aggressive forms and associated hematological malignancies are rarely reported.

After initial debate focusing mainly on the safety and efficacy profile of VIT in patients with mastocytosis [100], this treatment is now considered safe and efficacious [252,255,256], inducing protection from severe allergic reactions to subsequent stings.

Given reports of life-threatening and even fatal reactions to hymenoptera stings after discontinuation of treatment, long-term VIT (probably lifelong) may be recommended [100,203]. Patients not adequately protected by the usual maintenance dose of 100 µg should have their dose increased to 200 µg [252]. Patients affected by systemic mastocytosis with a history of anaphylaxis should always carry 2 adrenaline autoinjectors. This recommendation is also valid for patients receiving VIT [252].

Professional Aspects

Hymenoptera stings are the most frequent cause of occupational anaphylaxis and can be attributed to a specific work environment [257].

Since exposure to repeated stings is a key factor for the development of allergic reactions, persons working outdoors or in environments where hymenoptera live are considered to be at high risk. In addition to beekeepers [13], for whom a specific risk is recognized, other workers such as foresters, farmers, gardeners, truck drivers, masons, and electricians [258,259] also experience systemic reactions more frequently, as do greenhouse workers, who are exposed to bumblebee stings [8,260]. For these categories, hymenoptera venom allergy can be considered an occupational disease [259,261] necessitating specific primary prevention measures [262]. Hymenoptera venom allergy is a recognized cause of work disability that can require a worker to change or leave his/her profession in order to reduce the risk of exposure [263].

Given its degree of effectiveness, VIT is also recommended for moderate systemic reactions to enable the worker at risk to continue working [14,190,257,262].

Some European authors recommend verifying the efficacy of treatment through sting challenge before the resumption of work [262], although this clinical practice is not currently permitted in Italy. A maintenance dose of 200 µg may be indicated for beekeepers [73]. Persons with occupational bumblebee-induced anaphylaxis have a low degree of cross-reactivity with bee venom and therefore should undergo VIT with bumblebee venom [8]. Since workers who are frequently exposed to stings have a higher risk of relapse after discontinuation of VIT, some experts recommend continuing treatment for as long as the patient is at risk owing to his/her profession [262].

A recent Italian study conducted on 184 patients with anaphylactic reactions to hymenoptera venom showed an occupational cause in 17.4% of cases; of these, 71.8% continued to work after having received VIT. Re-stung workers (31.2%) were effectively protected [261]. The impact of VIT on professional activity increases with occupational risk [263].

Quality of Life

A history of previous allergic reactions to hymenoptera has a negative influence on the quality of life of affected patients. Many live their lives in constant anxiety about being stung and

experiencing the same or even more severe and potentially fatal reactions [264].

Questionnaires were validated to specifically evaluate the quality of life of persons allergic to vespids [151,265], including *P dominula*, in the Mediterranean area [266]. Randomized controlled clinical trials evaluating the impact of hymenoptera venom allergy on quality of life confirmed that immunotherapy is associated with a significant improvement in quality of life 1 year after initiation of therapy [151,267].

People undergoing immunotherapy have a better quality of life than those who are only prescribed the adrenaline autoinjector, even if they experienced a systemic reaction of medium severity such as urticaria or angioedema. Moreover, sting challenge results in a significant improvement in disease-specific quality of life in patients allergic to hymenoptera venom receiving VIT [265-268].

These findings should be taken into account when choosing whether to start immunotherapy in persons who experienced a cutaneous systemic reaction, and in some cases, immunotherapy should be preferred to the prescription of adrenaline autoinjectors alone [81].

In the case of children allergic to hymenoptera venom, the disease can have an impact on the quality of life of their parents. Through specific questionnaires, it was shown that parents of hymenoptera venom–allergic children have a worse quality of life: in addition to feeling responsible for the life and health of their children, parents fear the severe consequences of a sting [269].

Conclusions

The severity of allergic reactions to hymenoptera stings varies considerably and can sometimes be fatal. Although the epidemiological burden of hymenoptera venom allergy is similar to that of food allergy, awareness of this problem is poor in the general population and among health care providers and political decision-makers. Similarly, the availability of acute emergency treatment (adrenaline autoinjector) and long-term immunotherapy modifying the natural history of this allergy remains poor. This observation is somewhat paradoxical considering the numerous scientific innovations in this field over the past 5-10 years.

It is therefore mandatory to improve both knowledge and management of this condition and to ensure that clinicians are aware that VIT is by far the most effective form of allergen-specific immunotherapy available.

This consensus document should be made accessible to health care professionals and to anyone looking for information on allergic reactions to hymenoptera venom. It provides practical advice supported by scientific evidence on both diagnosis and therapy and can be used by specialists in daily clinical practice.

As in many other areas of medicine, studies performed in the coming years [90,151] will provide data that will facilitate the treatment of allergic patients.

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Conflicts of Interest

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