

SPECIAL ARTICLE

Emergency treatment of allergic reactions to Hymenoptera stings

U. MÜLLER, H. MOSBECH, P. BLAAUW, S. DREBORG, H. J. MALLING, B. PRZYBILLA, R. URBANEK, E. PASTORELLO, M. BLANCA, J. BOUSQUET, R. JARISCH and L. YOULTEN

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Summary

Allergic reactions to Hymenoptera stings are frequently observed all over Europe. Rarely they may induce long-standing morbidity or even be fatal. Several investigations have shown that the emergency treatment given to these patients is often inadequate. Cutaneous symptoms respond well to antihistamines and also to adrenaline. Adrenaline is the mainstay for outside hospital treatment of more severe reactions involving the respiratory tract (bronchial asthma, laryngeal oedema) and the cardiovascular system (anaphylactic shock). Inhaled adrenaline is especially useful in respiratory symptoms, while parenteral application of adrenaline is preferred for shock treatment. All patients with severe respiratory or cardiovascular reactions must be hospitalized, treated under intensive care conditions and observed for at least 24 hr. Emergency medications including adrenaline for inhalation or for self-injection must be given to all patients with a history of systemic allergic reactions to hymenoptera stings. These patients must also get instructions for safety measures to avoid further stings. They should be referred to an allergist in order to evaluate the indication for venom immunotherapy.

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Introduction

According to investigations in several European countries and elsewhere, 3–12% of the population give a history of large local or systemic reactions following Hymenoptera stings [1–6]. While large local reactions may sometimes last for weeks, most of the more threatening systemic reactions disappear within hours without sequelae. Long-standing morbidity due to myocardial or cerebral infarction may, however, occur, and fatalities have been reported from many countries [3, 7]. The annual number of deaths due to Hymenoptera stings is estimated to be about 40 for USA [8], 10 for Germany [9], five for England [10], three for Switzerland [3], two for the Netherlands [11] and one for Denmark [12], but may in fact be considerably higher. This was at least suggested by several authors investigating post-mortem sera from sudden unexpected outdoor deaths [13, 14], where IgE

antibodies to Hymenoptera venoms were frequently found.

According to studies on patients who died after Hymenoptera stings [10, 12, 15] death occurred within 1 hr in the vast majority of these patients, most often after a single sting. Late deaths were frequently associated with multiple stings or with severe hypoxic damage of the central nervous system after survival of the acute phase of anaphylaxis. Autopsy showed major alterations in the respiratory tract in about two out of three of the patients: laryngeal or bronchial obstruction by oedema and secretions, hyperinflation of the lungs, more rarely pulmonary haemorrhage or oedema. In the remaining patients the major pathological findings were located in the cardiovascular or central nervous system. Here generalized oedema, vascular congestion and haemorrhages were prominent. Acute myocardial infarction was observed in 5% of Barnard's cases [15].

The pathophysiologic events most likely responsible for these findings are: allergen-induced, IgE-mediated release of histamine, leukotrienes, prostaglandins and

Correspondence: Dr U. Müller, Chefarzt, Medizinische Klinik, Zieglerspital, Postfach 8965, CH 3007 Bern, Switzerland.

other mediators from mast cells and basophils. This results in: (i) vascular leakage and peripheral vasodilatation leading to fluid sequestration and consequently to hypovolaemic shock; (ii) disseminated intravascular coagulation [16,17] which may cause generalized haemorrhages and aggravate the hypovolaemic state; and (iii) hypoxia induced by bronchial obstruction and direct cardiotoxicity of mediators [18] that are responsible for cardiac failure or arrhythmias and contribute also to shock symptoms. Release of secondary mediators from inflammatory cells like eosinophils, neutrophils or macrophages is probably responsible for the rare late symptoms in biphasic or protracted anaphylaxis [19]. Pre-existing pathologic conditions are often found in Hymenoptera sting deaths and are likely to contribute to the fatal course. Thus in coronary heart disease, stenosis of coronary vessels will aggravate myocardial ischaemia and favour the development of infarction or arrhythmias. Moreover, it has been shown that in coronary heart disease mast cell numbers around coronary arteries are increased. 'Cardiac anaphylaxis' involving mediator release from these cells may contribute to acute myocardial failure [18].

As a consequence of this knowledge on the pathogenesis and course of life-threatening allergic reactions to Hymenoptera stings, treatment of these reactions must start as early as possible with medications that have an immediate effect on the major pathophysiologic events. Several retrospective investigations have shown that the emergency treatment actually given to patients with Hymenoptera sting reactions does often not fulfil these criteria [20–22]. Because of the infrequency and the extremely acute course of anaphylactic reactions, controlled studies on their treatment do not exist. Our recommendations must therefore be based on knowledge gained from (i) controlled studies on the treatment of other type I allergies like bronchial asthma; (ii) anecdotal observations which often originate from patients who develop anaphylactic or anaphylactoid reactions during general anaesthesia; and (iii) animal experiments.

Medications recommended for the treatment of acute allergic reactions

Adrenaline and other sympathomimetic drugs

By stimulation of adrenergic α -receptors, adrenaline induces vasoconstriction mainly in the range of arterioles, thus raises blood pressure and diminishes further capillary leakage. By stimulation of β -1-receptors, adrenaline has a positive inotropic and chronotropic effect on the heart and by β -2-stimulation it leads to bronchodilation. By enhancing production of cyclic AMP in mast cells and other inflammatory cells it impairs synthesis and

release of mediator substances. All these properties together explain the favourable effect of adrenaline on the most important symptoms of anaphylaxis like: drop in blood pressure, bronchial obstruction, angio-oedema and urticaria [23–25].

Adrenaline is immediately effective after intravenous injection and within a few seconds to minutes after intramuscular or subcutaneous application. Absorption seems to be more rapid and constant following s.c. injection in the upper arm than in the thigh [26,27]. Following inhalation an immediate effect can be expected on bronchospasm and mucosal oedema of the respiratory tract. After correct inhalation of 10–20 puffs of adrenaline by a metered-dose inhaler a significant increase of serum levels together with tachycardia and raise in systolic blood pressure as evidence of systemic adrenaline effects, has been observed in two studies [26,27].

Intratracheal application of adrenaline was recommended by Roberts [28]. According to another study, the absorption of adrenaline given by this route is unreliable in patients who are resuscitated for cardiac arrest [29].

When given intravenously, adrenaline may induce myocardial ischaemia and serious arrhythmias, especially in patients with pre-existing coronary heart disease. Ventricular fibrillation and myocardial infarction after intravenous application of adrenaline during anaphylactic shock may in some instances rather be caused by the drug than the allergic reaction itself [3,30–32]. Therefore intravenous application of adrenaline must be restricted to the treatment of severe shock and cardiac arrest. In this situation it is best given by continuous intravenous infusion of 5–20 $\mu\text{g}/\text{min}$ or else by slow injection of 0.5 mg in 10 ml solution over several minutes. ECG monitoring is indicated. In all other cases subcutaneous or intramuscular injection or inhalation are preferable. Owing to the short plasma half-life of adrenaline, injections or inhalations may have to be repeated at 10–20-min intervals. Adrenaline doses have to be adjusted according to body weight in children.

Beta-2-stimulants like salbutamol or terbutaline by inhalation or in severe cases by infusion are valuable in the treatment of bronchial obstruction. In severe protracted shock, besides adrenaline and volume substitution, vasopressor drugs like noradrenaline [33] or dopamine [34] may be indicated.

Antihistamines

H₁-antihistamines inhibit histamine induced constriction of non-striated muscles of bronchi, blood vessels and intestine and its increasing effect on vascular permeability by competitive binding to receptors. H₂-antihistamines antagonize stimulation of secretion induced by histamine.

Cardiac effects of histamine, especially coronary vasoconstriction and increased automaticity as well as peripheral vasodilation are mediated through both H_1 and H_2 receptors [23].

While a preventive effect of combined H_1 and H_2 blockers has been demonstrated in a controlled study [35], the therapeutic effect of such a combination is based on theoretical considerations [18,33,36] and occasional anecdotal reports [37,38].

When given intravenously, antihistamines have an immediate effect. This may however be insufficient to antagonize the massive histamine release during acute anaphylaxis when preparations currently available for parenteral application are used. Rapid i.v. injection of antihistamines may provoke delirious states and hypotension. Therefore, i.v. antihistamines have to be injected slowly over several minutes.

A better effect may be expected once the more potent anti-histamines of the new generation are available for parenteral use. When given orally, antihistamines are only effective after 15–30 min at the earliest. When they are taken immediately after the sting they can thus protect patients with a long reaction time between sting and symptoms. Their effect will come too late for the majority of patients to prevent symptoms although it may alleviate them.

Corticosteroids

By induction of lipocortine the corticosteroids inhibit membrane phospholipases and thus the generation of lipid mediators like prostaglandines, leukotrienes and the platelet-activating factor. They further inhibit synthesis of kinins and mediator release from inflammatory cells. Finally their presence is required for optimal efficacy of sympathomimetic drugs. In severe shock endogenous release of adrenocortical hormones may be insufficient [24,39].

In controlled studies on bronchial asthma a beneficial effect of treatment with corticosteroids by the intravenous route could not be observed before 1–4 hr after application [40,41]. Most likely, corticosteroids have therefore no influence on the survival of acute anaphylaxis. Corticosteroids have been shown to suppress the late IgE-mediated reaction in the skin [42] and the lung [43]. No controlled studies on the effect of corticosteroids in anaphylaxis are available. Although in one uncontrolled report [19] these drugs were unable to prevent biphasic or protracted anaphylaxis in several patients, we recommend their administration early in the course of anaphylaxis on the basis of the above mentioned controlled data in asthmatics.

Other drugs

Volume substitution with saline or plasma expanders is often essential to correct hypovolaemia due to the massive fluid sequestration by peripheral vasodilatation and vascular leakage. Correction of the pH with sodium bicarbonate is indicated in metabolic acidosis.

Glucagon has been recommended for the reversal of protracted anaphylactic shock under treatment with betablocking agents [18,44].

Intravenous theophyllin preparations may be added in protracted bronchial obstruction.

Treatment of various forms of allergic reactions to Hymenoptera stings

Cutaneous symptoms only (Table 1)

Many patients with Hymenoptera allergy develop cutaneous symptoms only. Large local reactions exceeding 10 cm in diameter and 24 hr in duration, urticaria or angio-oedema.

Large local reactions may appear 4–48 hr following a sting. Malaise and fever are commonly associated. These reactions are best treated with immobilization and elevation of the affected limb as well as application of cold packs or cold compresses [20]. Oral antihistamines may be effective if given early. In delayed large local reactions systemic or topical corticosteroids are most helpful [3].

In the presence of urticaria and angio-oedema H_1 antihistamines, preferably given by slow intravenous injection, are usually rapidly effective. To prevent protracted symptoms, corticosteroids are added. Adrenaline 0.3–0.5 mg subcutaneously is the treatment of choice in the U.S.A. and Australia, and also preferred by many European investigators [3,20,24,33]. Although there is no direct evidence from controlled studies that it is superior to parenteral H_1 antihistamines for treatment of purely cutaneous symptoms, experimental data and clinical experience suggest that adrenaline is both more rapid and more potent than antihistamines in antagonizing systemic allergic symptoms. The fact that any cutaneous reaction may proceed to involve the respiratory and/or cardiovascular system speaks further in favour of adrenaline. Advocates of antihistamines on the other hand point out the potentially serious side effects of adrenaline.

Patients with generalized cutaneous symptoms should stay under medical observation for at least 1 hr.

Respiratory symptoms (Table 2)

Bronchial obstruction is characterized by wheezing, cough and expiratory stridor, while symptoms like hoarseness, blurred speech, choking and inspiratory and

Table 1. Emergency treatment of cutaneous symptoms following Hymenoptera stings

Medical treatment	Other measures
Large local reaction H₁ antihistamine orally (e.g. terfenadine 120 mg b.i.d., clemastine 1 mg b.i.d., cetirizine 10 mg/day, loratadine 10 mg/day) until recovery Corticosteroid (e.g. prednisone 50–100 mg/day) orally until recovery	Cold packs Immobilization and elevation of affected limb Topical corticosteroids
Urticaria, angio-oedema, generalized erythema reaction H₁ antihistamine intravenously (e.g. clemastin 2 mg) <i>or</i> adrenaline 0.3–0.5 mg subcutaneously (in children 0.1 mg/10 kg body weight)* Corticosteroid intravenously (e.g. prednisolone 100 mg or methyl-prednisolone 80 mg)	Medical observation until condition improved, at least for 1 hr

* With protracted symptoms, adrenaline medication may be repeated every 10–20 min.

Table 2. Emergency treatment of respiratory symptoms during allergic reactions to Hymenoptera stings

Medical treatment	Other measures
Bronchial obstruction reaction Adrenaline 10–20 puffs from medihaler* <i>or</i> 0.3–0.5 mg subcutaneously* <i>or</i> beta-2-stimulator 4–10 puffs (e.g. salbutamol, terbutaline) In severe cases: salbutamol 5–10 µg/min intravenously Corticosteroids (e.g. prednisolone 100 mg) intravenously Aminophyllin 6 mg/kg over 20 min then 0.9 mg/kg per hr	Oxygen supply, medical observation until full recovery, in severe cases hospital admission, intubation or cricothyrotomy if needed
Laryngeal oedema reaction Adrenaline 10–20 puffs from medihaler <i>or</i> 0.3–0.5 mg subcutaneously* Corticosteroids (e.g. prednisolone 100 mg or methylprednisone 80 mg intravenously) Dosage for children: Adrenaline 0.1 mg/10 kg body weight, 2–4 puffs/10 kg body weight Prednisolone 20 mg/10 kg body weight	Same

* With protracted symptoms, adrenaline medication may be repeated every 10–20 min.

expiratory stridor point to laryngeal oedema. In the presence of respiratory symptoms adrenaline, given either by inhalation or subcutaneously, is the drug of choice. Because of the direct topical effect inhalation is preferred in this situation. In bronchial obstruction inhaled or—in very severe cases—i.v. beta-2-adrenergic drugs are a valid alternative and i.v. theophylline may be added. I.v. corticosteroids, although not immediately effective, should always be given. Further measures include oxygen supply and if needed intubation or cricothyrotomy [33]. The procedure for this intervention is summarized in Table 3.

Patients with respiratory symptoms must stay under

Table 3. Cricothyrotomy procedure (after 45)

- 1 Extend head
- 2 Locate cricoid cartilage
- 3 Make a small transverse incision in the skin in the anterior one-third of the cricothyroid space just above the upper border of the cricoid cartilage
- 4 Puncture the cricothyroid membrane in the midline
- 5 Enlarge the opening laterally with blunt dissection
- 6 Insert an endotracheal tube No 6 or No 7

Table 4. Emergency treatment of anaphylactic shock following Hymenoptera stings

Medication	Other measures
Emergency physician	
Adrenaline 0.3–0.5 mg intramuscularly (subcutaneously), in severe cases intravenously (0.5 mg in 10 ml over 5 min)*	Shock position
H ₁ and H ₂ antihistamine intravenously (e.g. clemastine 2 mg, ranitidine 100 mg)	If available: oxygen supply, i.v. infusion
Corticosteroids intravenously (e.g. prednisolone 100 mg)	Hospital admission
At the hospital	
Volume substitution (saline, plasma expanders)	Monitoring of ECG, arterial and central venous blood pressure, blood gases
pH correction (sodium bicarbonate)	
Pressor substances by continuous infusion (e.g.) adrenaline 5–20 µg/min, dopamine 100–1000 µg/min, noradrenaline 8–20 µg/min)	If needed: intubation, assisted ventilation, defibrillation, cardiac massage, intra-aortic balloon counterpulsation
Dosage for children	
Adrenaline and prednisolone, see Table 2	
Clemastine 1–2 mg intravenously	
Ranitidine 15 mg/10 kg body weight	

* With protracted symptoms adrenaline medication may be repeated every 10–20 min.

medical observation until recovered. In severe cases, especially when laryngeal oedema is present, hospital admission is recommended.

Gastrointestinal symptoms

Occasionally nausea, vomiting, diarrhoea or abdominal cramps may be predominant. Adrenaline s.c. is usually rapidly effective in this situation, while spasmolytic or analgesic drugs are of little help.

Anaphylactic shock (Table 4)

The emergency physician most often has to treat the patient with anaphylactic shock following a Hymenoptera sting at his or her office or even in the field. Facilities for treatment are restricted in this situation. First the patient will be brought to shock position and supplied with oxygen if available. Adrenaline is then given parenterally, preferably intramuscularly, in severe shock directly intravenously in a diluted form and over several minutes as described above. If available, an i.v. infusion with saline or a plasma expander is given and H₁ and H₂ antihistamines as well as corticosteroids are administered by this route. The patient is then hospitalized.

Further measures available to intensive hospital care are: monitoring of electrocardiogram, arterial and central venous blood pressure and the blood gases; if needed,

massive volume substitution, pH correction, intravenous pressor substances, intubation with assisted ventilation, defibrillation, intra-aortic balloon counterpulsation [37], etc. Because of the possibility of biphasic anaphylaxis, all patients with anaphylactic shock must be observed at the hospital until fully recovered, at least for 24 hr [19,20].

Especially severe and protracted anaphylactic shock may occur in patients on treatment with beta-blocker drugs [45]. Beta-adrenergic receptors normally control the release of allergic mediators. Beta blockade interferes with this regulatory mechanism by competition with endogenous catecholamines and also with the effect of beta-adrenergic agents given for treatment of anaphylaxis. Therefore higher and often repeated doses of adrenaline and other beta-adrenergic drugs must be given [45], together with i.v. H₁ antihistamines and corticosteroids. The use of H₂ antihistamines is controversial, because these drugs rarely may induce bradycardia and cimetidine also decreases the clearance of beta-blockers [45]. On the other hand, the beneficial effects of a combination of H₂ and H₁ antihistamines in anaphylaxis are suggested by several observations [35,37,38,48].

Emergency kits for self-medication

All patients with previous Hymenoptera sting reactions must receive emergency medications and carry them

Table 5. Adrenaline for self-medication

Brand name	Company	Dose (mg)	Application
Epipen	Center Labs	0.3	Subcutaneous
Epipen Jr	Center Labs	0.15	Subcutaneous
Anakit	Hollister-Stier	0.3	Subcutaneous, two doses
Min-I-Jet 0.5	IMS	0.5	Subcutaneous
Anahelp	Stallergenes	0.25	Subcutaneous, four doses
Fastjekt	Allergopharma	0.3	Intramuscular
Medihaler-Epi (Adrenaline-Medihaler)	3M Riker	0.15 mg/puff	10–20 inhalations

Table 6. Adrenaline self-injection kit *vs* adrenaline metered-dose inhaler

Properties	Self-injection kit	Metered-dose inhaler
Patient compliance		
Readiness to use	+	+++
Correct use	Quite easy	Quite difficult
Effect on		
Respiratory symptoms	++	++++
Cardiovascular symptoms	++++	++
Use in unconscious patient	++	—
Absorption in shock	?	?
Shelf life	1 year	3 years

during the flying season of Hymenoptera. Tablet sets should contain an adequate dose of a rapidly absorbed oral antihistamine (e.g. terfenadine 120 mg, or loratadine 20 mg, or clemastine 2 mg, or cetirizine 20 mg) and a corticosteroid (e.g. prednisone 100 mg).

In addition, all patients with a history of systemic reactions following Hymenoptera stings must receive adrenaline. The various preparations for self-application are listed in Table 5. In the U.S.A., adrenaline self-injection kits are usually prescribed [47]. In Europe, adrenaline for inhalation (adrenaline medihaler[®]) has become increasingly popular in recent years [26,27]. In our experience, this form is more readily used by the patient than the self-injection kit, although correct application is more difficult. A good topical effect can be expected on respiratory symptoms, especially laryngeal oedema, which are thought to be responsible for two-thirds of Hymenoptera sting fatalities [15]. The shelf life of the inhaler is 3 years, compared with 1 year for self-injection kits. While absorption of inhaled adrenaline

may be reduced in shock, the same is true for adrenaline given subcutaneously. Advantages and disadvantages of the two application forms are given in Table 6. The application technique for both inhaled and injected adrenaline must be instructed carefully by the physician, preferably with placebo-containing devices. Subcutaneous injections are applied in the upper arm. The following inhalation technique is recommended: the aerosol puff is triggered at the beginning of a slow inspiration after a maximal expiration. Inspiration is then continued and the breath held at maximal inspiration for 10 sec. The patient should then breathe normally for 10 sec before the next inhalation [27].

A tourniquet to be applied proximally from the sting site is recommended by some and contained in the Anakit[®]. It is supposed to delay allergen absorption. The same effect can be expected from s.c. adrenaline if applied immediately directly at the sting site. Moreover, this way of administration may inhibit further mediator release locally. However, we do not recommend application of

Table 7. Precautions for patients with bee and vespid sting allergies

Avoid sudden movements when a bee or vespid approaches
Keep away from open flowers and over-ripe, fallen fruits
When gardening take special care: keep the body covered as much as possible, wearing a hat, gloves, long trousers and a shirt or blouse with long arms
Avoid using perfumes, hairsprays, strongly scented suncreams and shampoos
Avoid loose-fitting, light garments, black or brightly-coloured patterns. White, green and light brown are preferable
If eating out of doors leave no sweet things or meat or left-over food lying exposed
Sweat and carbon dioxide attract many stinging insects. Be very careful therefore if exercising or playing out of doors
Never walk barefooted: bees love clover and many vespids have their nests in the ground
Keep wastebins in and around the house clean and firmly closed
Avoid places where animals are fed. The left-overs attract bees and vespids. Do not disturb fallen tree trunks or logs: vespids often build their nests in these
Keep the windows in your bedroom closed during the daytime, or fit a mosquito net
Always carry your emergency treatment kit with you
Notify the local bee keeper or the fire brigade if bees swarm in your neighbourhood. The fire brigade may also remove vespid nests if asked to
If attacked by bees or vespids, cover your head with your arms or with a piece of clothing. Move away slowly, without any sudden movements, until safe
Wear a helmet and gloves when motorcycling

adrenaline before symptoms are present, because several prospective studies have shown that many patients, even with a history of severe systemic reactions, do not react again when re-stung [3,48–50], and also because of the short plasma half-life of this potentially harmful drug.

In case of a resting the patient must act as follows:

- (i) Remove stinger without squeezing venom sac.
- (ii) Take emergency tablets immediately, prepare adrenaline for use.
- (iii) As soon as any systemic symptoms arise: apply adrenaline subcutaneously or by inhalation (dosage see Table 2).
- (iv) Seek medical attention.

All patients with a history of systemic reactions following Hymenoptera stings should be referred to the allergist, who will instruct them regarding safety measures to avoid further stings, such as given in Table 7. The allergist will also supply them with emergency medications and tell them how to use these. She or he will finally consider venom immunotherapy. The position paper of the European Academy of Allergology and Clinical Immunology [51] may serve as a guideline.

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