Mattioli 1885 | Issn 0397-9148 | Volume 40 N. 2 /2008 - June 2008

European Annals of Allergy and Clinical Immunology

THE OFFICIAL JOURNAL OF AAITO | ASSOCIAZIONE ITALIANA ALLERGOLOGI IMMUNOLOGI TERRITORIALI E OSPEDALIERI

2/2008

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The wasp-horsefly syndrome

Poste Italiane s.p.a. - Sped. in A. P. - D.L. 353/2003 (conv. in L. 27/02/2004 n. 46) art. 1, comma 1, Aut. n. 080038 del 11/06/2008 - DCB Parma - Pinito di stampare Giugno 2008

Printed in June 2008

The contents of this Journal are indexed in PubMed - U.S. National Library of Medicine and Embase/Excerpta Medica

European Annals of Allergy and Clinical Immunology

THE OFFICIAL JOURNAL OF AAITO -
ASSOCIAZIONE ITALIANA ALLERGOLOGI IMMUNOLOGI TERRITORIALI E OSPEDALIERI

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Tel. 0039-0524-84547
Fax 0039-(0)524-84751
E-mail: edit@mattioli1885.com

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Use of adrenaline in allergy

AAITO Committee for "Use of Adrenaline in Allergy Guidelines"

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Introduction

Anaphylaxis is a clinical syndrome that represents the most severe systemic allergic reaction and requires immediate treatment because of its potential fatal outcome.
Adrenaline is the recommended first line treatment for patients with severe anaphylaxis.
The aim of this document is to discuss the safety and efficacy of adrenaline in the treatment of anaphylaxis in the light of currently available evidence and to suggest a practical approach to the use of auto-injectors.
Anaphylaxis is a collection of symptoms affecting multiple systems that occur rapidly after an adequate stimulus (1) whose severity varies from mild to life-threatening or fatal and may be rapidly progressive. According to different studies, anaphylaxis is probably underestimated and underrecognized and conversely, self-injectable adrenaline is probably over-prescribed (2) but often underused (3).
In retrospective studies of individuals died from anaphylaxis, adrenaline has been consistently reported to be underused, and failure to use it at all, its delayed use, inappropriate dosage, or inappropriate route of administration have been identified as contributing factors to death (3, 4). In one autopsy series, although adrenaline was given in 62% of anaphylactic reactions triggered by a variety of agents, adrenaline had been given before respiratory arrest in only 14% of cases (3). In studies of patients surviving anaphylaxis episodes, only 30% to 40% of subjects who required adrenaline actually received it (5).
However, adrenaline is not a treatment without risk (4, 6) especially in individuals with some pre-existing cardiovascular disease or who are taking interacting medications (7). By contrast, myocardial ischemia and cardiac arrhythmias may occur in patients with anaphylaxis who don't receive adrenaline (8).
Prescribing self-injectable adrenaline requires a careful balance of advantages and disadvantages. When adrenaline is prescribed, a careful explanation of its benefits and its use should be provided.
Finally, it is not yet fully accepted that having this relatively expensive treatment improves quality of life of patients or of their relatives (9, 10).

1. Anaphylaxis

Even though anaphylaxis was first described about 100 years ago and it is one of the most alarming disorders in medicine, there is no universal agreement on its definition or diagnostic criteria . This has led to confusion in epidemiology, pathophysiology and treatment of this disorder.

1.1 Definition of anaphylaxis and criteria for diagnosis

Recently, experts from world wide allergologic scientific societies held a symposium to establish a universally accepted definition of anaphylaxis and clinical criteria to accurately identify cases of anaphylaxis (11).
According to this panel anaphylaxis is <u>likely</u> when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosa, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following
a) Respiratory failure (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b) Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly (minutes to several hours)after exposure to a *<u>likely</u> allergen for that patient* :
a) Involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)
b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c) Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
d) Persistent gastrointestinal symptoms (e.g. cramps, abdominal pain, vomiting)
3. Reduced BP after exposure to *<u>known</u> allergen for that patient* (minutes to several hours):
a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline *(PEF,* Peak expiratory flow; *BP,* blood pressure; *RR,* respiratory rate*; CR*, cardiac rate)
In table 1 the BP value to establish hypotension in a patient and the cardiac rates at rest in infants and children are reported.
The authors (11) assumed that the criteria proposed could encompass > 95% cases of anaphylaxis. Because the majority of anaphylactic reactions include skin symptoms, at least 80% of anaphylactic reactions should be identified by **Criterion 1.**
Criterion 2 includes gastrointestinal symptoms as a pertinent target of response because they have been associated

Table 1 - From Lieberman P. (12) with some modification

Age	Systolic blood pressure (mm Hg)	Cardiac rate
newborns (0-28 days)	< 60	From min 70' to max 190'
infants (1 – 12 months)	< 70	From min 80' to max 160'
children (1 to 10 years)	< 70 + (2 x age in years)	From min 80' to max 110'
Subjects older than 10 years	< 90	From min 65' to max 110' *

*max and min values of cardiac rate may show variations of +- 5 beats/ minute after the age of ten

with severe outcomes in various anaphylactic reactions and captures the cases (up to 20%) without skin symptoms, especially children with food allergy or insect sting allergy.

Criterion 3 should identify the rare patients who experience acute hypotension after exposure to a known allergen. Although the authors assumed that these criteria should accurately identify anaphylactic reactions in > 95% of cases (11), these criteria need to be validated by a prospective multicenter clinical survey.

As a grading system to indicate the severity of the anaphylactic reactions, the classification by Brown can be used (13); this classification is based on some clinical parameters that can be easily assessed:

• Bronchospasm
• Respiratory rate
• Blood pressure
• Glasgow Coma Score (Tab. 2)

Anaphylaxis is **mild** with a Glasgow Coma Score (GCS) > = 15, systolic BP >= 90 mm/Hg, and RR< 25. Anaphylaxis is worse in the presence of systolic BP<90 mmHg, RR > 25/min, and GCS<15.Confusion, collapse, unconsciousness associated with hypotension and hypoxia (systolic BP< 90 mmHg, RR>25/min, GCS <15) are associated with **severe anaphylaxis.** In this situation, myocardial ischemia, myocardial infarction, and fatal cardiac arrhythmias can be present (14, 15).

Table 2 - Glasgow Coma Score

The GCS is scored between 3 and 15, 3 being the worst, and 15 the best. It is composed of three parameters: Best Eye Response, Best Verbal Response, Best Motor Response, as given below:

Best Eye Response (4)
1. No eye opening
2. Eye opening to pain
3. Eye opening to verbal command
4. Eyes open spontaneously

Best Verbal Response (5)
1. No verbal response
2. Incomprehensible sounds
3. Inappropriate words
4. Confused
5. Orientated

Best Motor Response (6)
1. No motor response
2. Extension to pain
3. Flexion to pain
4. Withdrawal from pain
5. Localising pain
6. Obeys Commands

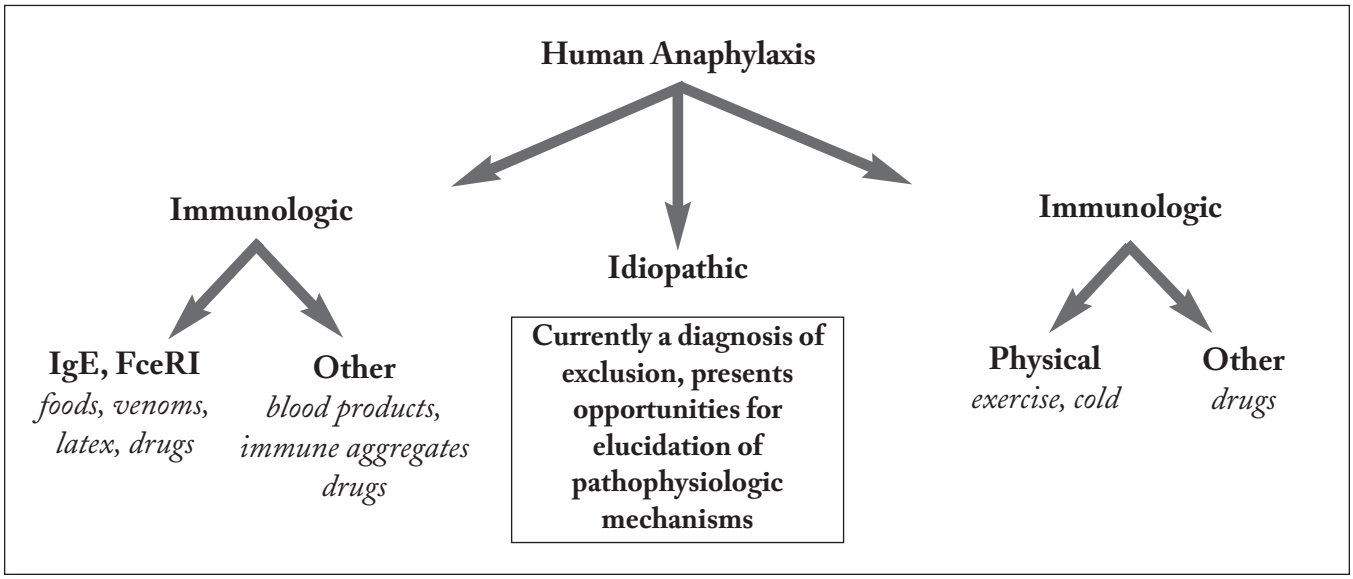
Note that the phrase 'GCS of 11' is essentially meaningless, and it is important to break the figure down into its components, such as E3V3M5 = GCS 11. A Coma Score of 13 or higher correlates with a mild brain injury, 9 to 12 is a moderate injury and 8 or less a severe brain injury.

Teasdale G, Jennett B, Lancet (ii) 81-83, 1974.

1.2 Pathogenetic mechanisms and triggers

The essential mechanism underlying anaphylaxis is the presence of biologically active chemical mediators released from mast cells or basophils (16). If this occurs in the context of a classic IgE mediated reaction from previously sensitized mast cells or basophils, then **anaphylactic reaction** is the preferred term. Degranulation of mast cells or basophils may also occur by non-IgE mediated mechanisms; in these cases the term **anaphylactoid reactions is generally used**. Clinically it is not possible to distinguish the two types of reaction, and treatments for both mechanisms are identical but the triggers must be accurately investigated. In fact, invalid assumptions of an anaphylactoid cause have led to fatal re-exposure (17).

Figure 1 - From Simons modif. 17



According to underlying mechanisms, anaphylaxis can be divided in immunologic, non immunologic or idiopatic as summarized in figure 1.

In the presence of idiopatic anaphylaxis, wich can accounts for up two thirds of the episodes, novel triggers can be identified or an underlying potentially severe disease (e.g. mastocytosis) must be suspected (18). Idiopathic anaphylaxis is diagnosed only after other causes of anaphylaxis have been excluded and other differential diagnoses have been considered.

The triggers of an anaphylactic reaction , either immunologic or non-immunologic, are very numerous (Tab. 3) (12-17).

1.3 Clinical features

Anaphylaxis can include any combination of common signs and symptoms (as previously described in paragraph 1.1) (19, 20). Clinical manifestations of anaphylaxis depend on sensitivity of the subject (presence of internal or external enhancing factors), dose, time and route of exposition to the trigger. Symptoms may develop within seconds to a few hours after the offending stimulus, with the vast majority of reactions developing within the first hour. The more rapidly anaphylaxis develops, the more likely the reaction will be severe and potentially life-threatening. Moreover, symptoms that are not immediately life-threatening might progress rapidly unless

Table 3 - From Simons FE (17), modified

A. Allergen triggers (IgE-dependent immunologic mechanism)

1) Foods, especially peanut, tree nut, seafood, fin fish, milk, egg)
2) Insect (Hymenoptera) venoms
3) Natural rubber latex
4) Medications (e.g. β-lactam antibiotics)
5) Biologic materials, including allergens, vaccines, and hormones (e.g. progesterone)
6) Food additives, including spices, insect-derived colorants (e.g. carmine), and vegetable gums
7) Seminal fluid
8) Occupational allergens
9) Novel or unusual allergens:
   - Foods: vegetables, fruits, lupin flour, mites, bird's nest soup
   - Biting insect saliva: mosquitoes, pigeon ticks, triatomid bugs, green ants
   - Venoms: jellyfish, scorpions, snakes
   - Medications and biologic agents: Botox, bee products, herbal formulations

B. Nonallergen triggers (IgE-independent, formerly classified as anaphylactoid, reactions)

1) Physical factors (e.g. exercise, cold, heat, sunlight/UV radiation
2) Medications (e.g. opiates)
3) Ethanol
4) Iodinated contrast media

treated promptly and appropriately (12). Fatal anaphylaxis develops in more than three quarters of cases within 15 minutes following the triggering stimulus. Pumphrey reported as average time to the respiratory arrest in presence of severe anaphylaxis 30 minutes for food anaphylaxis, 15 for insect venom anaphylaxis and 5 in the case of drugs (3).

The cardinal clinical feature of cardiovascular compromise during anaphylaxis is hypotension, associated with vasodilatation or a rapid onset of shock with peripheral circulatory failure. In some cases, besides diaphoresis and loss of consciousness, bradycardia can occur. This may lead to an erroneous diagnosis of lypotimia or myocardial infarction. These cases are normally poorly responsive to adrenaline, lack alerting cutaneous symptoms and require a rapid and correct differential diagnosis for an immediate resuscitatory intervention (14).

The prevalence of asthma in pediatric anaphylaxis cases is significantly higher than in the general population. Anaphylaxis may occur in absence of alerting cutaneous features. In children with anaphylaxis, respiratory abnormalities are the predominant finding, in comparison to adults in whom cardiovascular instability appears more commonly (21).

Up to 20% of adults and up to one third of children with severe anaphylaxis will experience a biphasic response. In case of ***biphasic anaphylaxis***, patients develop classical symptoms, seem to recover (and may even become asynptomatic), and then experience a recurrence of symptoms in absence of further exposition to offending stimulus. The intervening quiescent period lasts up to 2 to 8 hours (22, 23).

Rarely, the anaphylactic reaction may be protracted, lasting for more than 24 hours. ***Protracted anaphylaxis*** is associated in 25% of the cases to assumption of oral medical treatments or food and often may be life-threatening situation, the symptoms lasting up to three weeks (1, 24).

Until methods are developed to predict or avoid biphasic or protracted anaphylactic reactions, all patients should be observed for several hours (8-10) after apparent recovery from acute anaphylaxis.

1.4 Differential diagnosis

In case of suspected anaphylaxis, when a history of an offending agent is not clear-cutor or a history cannot be obtained at all, differential diagnosis has to consider several systemic disorders which share clinical features of anaphylaxis and which may be life-threatening (Tab. 4) (12, 25, 26).

Table 4 - Differential Diagnosis for Anaphylaxis. From Tang AW (19), modified

Presentation	Differential diagnosis
Hypotension	Septic shock Cardiogenic shock Hypovolemic shock
Respiratory distress with wheezing or stridor	Airway foreign body Asthma and chronic obstructive pulmonary disease exacerbation Vocal chord dysfunction syndrome
Postprandial collapse	Monosodium glutamate ingestion Sgombroid syndrome
Flush syndrome	Carcinoid Postmenopausal hot flushes Red man syndrome (vancomycin [Vancocin]) Ethanol
Miscellaneous	Panic attacks Systemic mastocytosis Hereditary angioedema

1.5 Prevalence and risk factors

Retrospective epidemiologic studies have been performed in Olmsted County, Minnesota, from 1983 to 1987 (27), in Australia on a wide pediatric population (28), and in Washington on children and adolescents enrolled in the years 1991-1997 (29). The reported data suggest that anaphylaxis is diagnosed with relevant differences depending on diagnostic criteria. Coding according to international classification of disease ICD9CM specific to identify anaphylactic episodes, brings to an estimated incidence of 10.5 cases per100,000 person per year (95% CI, 8.1-13.3 per 100,000 person/year). Clark (30) reported that the most important risk factor for fatal anaphylaxis is represented by an age of 15-17 years, with males being more frequently affected than females. The most important triggering agent was food (peanuts, hazelnut, fish, and seafood). Different Authors report an incidence ranging from 8 to 21 new cases per 100,000 subjects per year according the studied age, with a risk of fatalities between 0.6 and 1% (31).

The prevalence (new cases plus relapses) seems stable over the years, ranging between 30 and 60 cases/100,000 subjects/year (32). Moneret-Vautrin (33) reports life-threatening anaphylaxis in 1-3 patients per 10,000 medical examinations, with even greater values in USA and in Australia. The incidence of severe anaphylaxis with cardiovascular collapse, evaluated in the Canton of Bern, Switzerland, is calculated as 7.9-9.6 per 100,000 inhabitants per year, 59% of the cases being due to insect stings, 18% to drugs and 10% to food (34).
In a recent review based on various epidemiological studies, the incidence of anaphylaxis was calculated as 2% in the general population (35). In a study on 38,685 patients who were referred to the emergency department of a general hospital in Milan during 1997-1998, 140 cases of anaphylactic reactions (13 with loss of consciousness) occurred with an incidence of 0.4% (36).
Anaphylaxis can be over-estimated if the diagnosis is performed with different criteria (see diagnostic criteria); on the contrary it might be under-recognized because symptoms are not carefully reported by many First Aid units (17).
Regarding risk factors, many Authors emphasize the age of patients as the most important factor for the severity of reactions: in fact the greatest incidence of fatalities is observed in people 54-67 years old for drug and insect stings-induced anaphylaxis; regarding food, the most frequently affected age is between 22 and 24 years (15, 37). Age seems also to influence the causes of anaphylaxis: in children foods represent the most important trigger followed by hymenoptera and drugs. Conversely, this sequence is reversed if all the ages are considered, with hymenoptera being the most important cause of anaphylaxis, followed by foods and drugs (38). Lately, Italian epidemiologic data are actively recorded by the Observatory for the severe allergic reactions of the Allergy Network of the Piemonte Region. A total of 686 anaphylaxis diagnoses have been collected by the Observatory from January 2004 to June 2005: 60% were associated with hymenoptera stings, 24%with food, 9% with unknown causes, 4.1% with drugs, 1,5% with FEIA (Food Exercise Induced Anaphylaxis); 1.3% cases were idiopatic and 0.1% biphasic (39,40).
Atopy and /or asthma represent the most important risk factors for idiopatic anaphylaxis, as well as for FEIA, food anaphylaxis, latex-induced and radiographic contrast media-induced anaphylaxis; conversely these are not risk factors for anaphylaxis induced by β-lactams, insect venom, insulin and miorelaxants (41, 42)

Literature data suggest that the following patients have to be considered at highest risk for anafhylaxis:
1. patients with ill-controlled bronchial asthma (4)*
2. patients experiencing anaphylaxis following the ingestion of very low amounts of food (4)
3. patients allergic to particular foods (peanuts, nuts and seeds, fish, and seafood) (43)
4. patients with exercise induced anaphylaxis (42)
5. patients with difficulties to reach a First Aid dept.
6. patients with mastocytosis (44)
7. patients with very high level of total IgE (>10,000 KU/l) (45)
8. patients taking beta-blockers or ACE inhibitors (because of the difficulty in managing anaphylaxis) (46)
9. children (and adults) with atopic dermatitis (47)
10. children > 5 years old (90% of fatalities occur at a school age) (48), and adolescents (43)

* the poorly controlled severe asthma is an important factor of risk for death

1.6 Factors interfering with recognition and treatment of anaphylaxis

The risk of anaphylaxis, its recognition and its treatment may be influenced by pharmacologic treatments, abuse of drugs, and by particular personal situation of the patient, as summarized in the table 5 (17).

2. Adrenaline

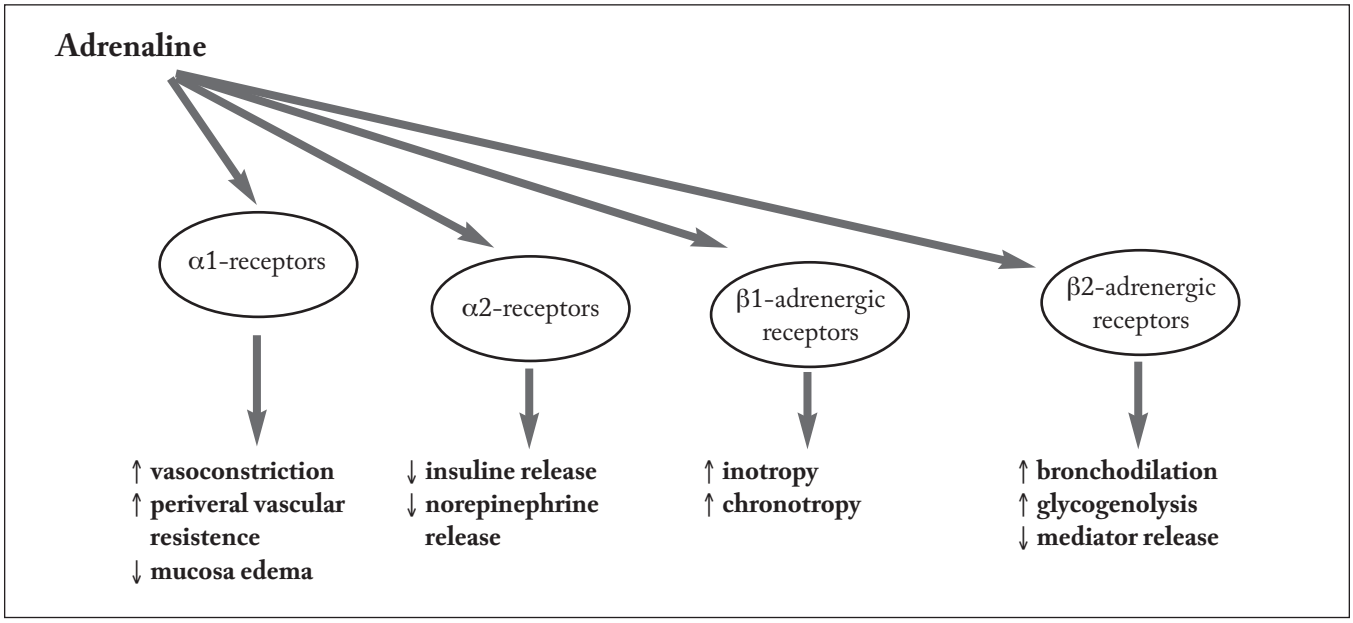
Adrenaline has been considered effective in the treatment of the anaphylactic shock since 1925 (49).
Adrenaline is a direct-acting sympathomimetic α-adrenergic and β-adrenergic agonist with cyclic adenophosphate-mediated complex, bidirectional pharmacologic effects on many target organs. Achieving high plasma and tissue adrenaline concentrations rapidly, appears to be critical for reversal of hypotension and possibly for survival.
Administered to individuals of any age, in therapeutic doses, it may cause pharmacologic adverse effects such as anxiety, fear, restlessness, headache, dizziness, palpitation, pallor and tremor. Rarely, and especially after overdose, it may lead to ventricular arrhythmias, angina, myocardial infarction, pulmonary edema, sudden sharp increase in blood pressure, and intracranial hemorrhage.
There is, however, no absolute contraindication to adrenaline use in anaphylactic shock (50).
Figure 2 shows the most important pharmacological effects of adrenaline.

Table 5 - Comorbidities and concurrent therapies: from Simons FE (17)

Might interfere with recognition of trigger or symptoms	Might affect treatment
Comorbidities	
Impairment of vision or hearing	Asthma
Neurologic disease	Cardiovascular disease
Psychiatric disease (eg, depression, ADHD)	Lack of coordination or strength (inability to self-inject epinephrine)
Developmental delay	
Behavior problem	
Substance abuse	
Concurrently administered medications	
Sedatives (eg, sedating H_1 -antihistamines)	β-Adrenergic blockers*
Hypnotics	α-Adrenergic blockers*
Ethanol	Angiotensin-converting enzyme inhibitors†
Recreational drugs	Angiotensin II receptor blockers†
	Tricyclic antidepressants‡
	Monoamine oxidase inhibitors‡
	ADHD§ medications (eg, amphetamines, methylphenidate)

ADHD, Attention deficit–hyperactivity disorder.
* Regardless of route of administration; potentially decrease epinephrine efficacy by blocking effects at adrenergic receptors.
† Potential interference with endogenous compensatory responses.
‡ Potential increase in adverse effects of epinephrine because of prevention of epinephrine uptake at adrenergic receptors.
§ Side effects are similar to those of epinephrine; amphetamines and methylphenidate release intracellular stores of epinephrine and also block monoamine oxidase, preventing epinephrine uptake at adrenergic receptors.

Figure 2 - Pharmacology of adrenaline. From Simons FE (2), modified



Pharmacology of adrenaline. In anaphylaxis, drug's α1-adrenergic effects (vasoconstriction, increased peripheral vascular resistance, and decreased mucosal edema) and some of its β2-adrenergic effects (bronchodilation and decreased mediator release from mast cells and basophils) are of primary importance. Low adrenaline concentration may paradoxically enhance release of histamine and other mediators from mast cells and basophils and result in vasodilation.

2.1 Safety

The use of adrenaline is safe: its inappropriate use may be dangerous, especially in case of overdose (relative or absolute) and bolus intravenous administration (51).
The risk of epinephrine adverse effects may be increased in individuals with some pre-existing cardiovascular, central nervous system, or thyroid diseases.
It must be stressed that the risk of acute myocardial ischemia during anaphylaxis is particularly elevated in patients who show a marked hypotension as the most important symptom; in this case it isn't possible to avoid adrenaline, even in a cardiac patient (12).
The risk of adverse effects may be also increased in persons using monoamine oxidase inhibitors, which block adrenaline metabolism, or in those using tricyclic antidepressants or cocaine, in whom adrenaline duration of action is prolonged.
Prospective, randomized, double-blind, placebo-controlled clinical trials of epinephrine in individuals actually experiencing anaphylaxis are unethical because prompt treatment with epinephrine is deemed critically important for survival. Also, such studies would be difficult to conduct because anaphylaxys episodes occur without warning in a nonmedical setting and differ in severity among individuals and from one episode to another in the same individual.
Despite the absence of clinical trials, evidence from clinical pharmacology studies, epidemiologic studies and other investigations support the use of adrenaline in anaphylaxis at the recommended dosage, administered as intramuscular injection. Based on current evidence, the benefit of using appropriate doses of intramuscular adrenaline far exceeds the risks (**grade C**).

2.2 Routes of administration

Studies of kinetics of adrenaline are performed in patients with a history of previous anaphylaxis but in a good health at the moment of the study with an unaffected cardiovascular system. Conversely, the cardiovascular system may be importantly affected during the anaphylactic episode: this may lead to a different distribution into the tissues of adrenaline.
The most effective route of administration is **intramuscular** (52) which allows to reach more rapidly plasmatic concentrations that are significantly higher than those obtained by subcutaneous injection (**grade B**). Adrenaline subcutaneous injection results in a powerful vasoconstrictor effect. Retention of epinephrine at the site of injection might lead to a delayed absorption into systemic circulation.
Peak plasma adrenaline concentrations are significantly higher after injection in the vastus lateralis muscle, probably due to its large size and excellent blood supply, compared with the injection in deltoid muscle, or placebo injection (52). In many overweighed patients, even children, it is important to use needles longer than 2,5 cm to avoid a subcutaneous injection of adrenaline (53).
Inhalation of epinephrine from a **pressurized metered-dose inhaler** (non present in Italy) will be inadequate for treatment of non-respiratory symptoms. Comparative studies of the inhalatory and intramuscular administration of adrenaline during anaphylaxis are lacking. (54, 55).
Intravenous adrenaline has been associated with the induction of fatal cardiac arrhythmias and myocardial infarction (56). Major adverse effects usually occur when adrenaline is given too rapidly, inadequately diluted, or in excessive dose (**grade C**). Such published reports often fail to state clearly that other factors, including hypoxia, acidosis, or the direct effect of inflammatory mediators, may be, at least in part, responsible for the cardiovascular complications. Given all of this, the intravenous route should be reserved for those with unresponsive anaphylaxis. This includes any patient who deteriorates despite receiving intramuscular adrenaline or those in whom there is a doubt about the circulation. It should only be given in a resuscitation area during electrocardiography by medical staff who are trained in its use (**grade C**) (7).
The possibility to administer adrenaline as **sublingual fast-disintegrating tablets** is under investigation. Studies are being performed on the dose required to achieve epinephrine plasma concentrations similar to those obtained after epinephrine 0.3 mg intramuscular injection (57).

2.3 Dose

Some disagreement exists about the recommended dose of adrenaline. North American guidelines suggest a dose of 0.3-0.5 ml diluted 1:1000 (0.3-0.5mg) in adults, whereas European literature suggests 0.5-1.0 mg. No comparative trials have been conducted.
Almost all of the literature agrees on 0.01 mg/kg in infants and children, even in those who weigh > 50 kg (10).
For most patients only one dose is needed, although repeated doses may be given at 5 minutes intervals until symptoms improve.

In summary, recommendations for epinephrine dosing in the first-aid, out-of-hospital treatment of anaphylaxis are based on anecdotal experience and vary with regard to maximum initial dose (0.2 mg to 0.5 mg in adults; 0.01 mg/kg to a maximum of 0.3 mg in children), and interval between doses (5-30 minutes) (2).
In case of persistent hypotension, continuous intravenous infusion may be used at a dose of 100 mcg /ml and 1 mcg/minute, increasing, if necessary 10 mcg, in a resuscitation area with a trained staff (58).

2.4 Drug interactions

Anaphylaxis may be made worse by β- blockers, and these drugs decrease the effectiveness of adrenaline (**grade C**). (12,59) Paradoxically, the dose of adrenaline should be halved owing to the increased risks associated with unopposed stimulation of α- adrenoceptors and reflex vagotonic effects, including bradycardia, hypertension, coronary artery constriction, and bronchoconstriction (60). Thus, all β-blockers, including eye drops, should be withdrawn and substituted in patients considered at risk of anaphylaxis (61).
In case of Hymenoptera venom allergy the side-effects during desensitization and the capacity by the vaccine to protect at the moment of the re-stinging did not differ in patients using beta-blockers or different therapies(62). Recent European Guidelines (63) focus therefore on the importance to evaluate the risk of cardiac disturbances in patients with heart diseases if β-blockers are avoided during immunotherapy and the risk to develop a reaction during specific immunotherapy.
In case of anaphylaxis in patients using β-blockers, glucagon is believed to be able to resolve protracted hypotension and bronchospasm during anaphylaxis, by mechanisms that are not yet completely understood (64).
Tricyclic antidepressants and monoamine oxidase inhibitors potentiate adrenaline and increase the risk of cardiac arrhythmias. The dose of adrenaline should be halved in these patients (**grade C**) (18). Cocaine sensitizes the heart to catecholamines (as does uncontrolled hyperthyroidism), and adrenaline is therefore relatively contraindicated (**grade C**).
As shown in autoptical studies, lying down (Trendelemburg's position is best) during an anaphylactic episode is crucial for a good outcome. Patients thought to be at risk of anaphylaxis and those who might be involved in their care (teachers, babysitters, spouses, friends, and coworkers) should be told of the need to remain lying down if they feel faint during a reaction, unless there is a greater need to sit up to overcome difficulty in breathing (65).

2.5 Bad outcomes

Adrenaline is usually effective in the first-aid treatment of anaphylaxis.
Evidence in the literature suggests that a poor outcome is associated with late administration of adrenaline, inappropriate dosage and incorrect way of administration (49). In a series of 13 fatal and near fatal anaphylactic reactions over a 14 months period, only two of the six patients who died received adrenaline within the first hour compared with six of the seven survivors (**grade C**) (7). In a retrospective study of 27 patients with anaphylaxis occurring outside hospital, all those treated within 30 minutes recovered compared with two deaths in subjects whose treatment was delayed by more than 45 minutes (**grade C**) (7). One study showed that adrenaline was used in the treatment of 62% of fatal reactions but it was used only in 14% before cardiac arrest (**grade C**) (3). This may, however, be due in some part to both the speed of reactions and the availability of treatment. As a result, current guidelines recommend adrenaline to be given as soon as possible (7).
The severity of a previous reactions does not determine the severity of future reactions, and subsequent reactions could be the same, better, or worse. The unpredictability depends on the degree of allergy and the dose of allergen. A series of pediatric anaphylaxis showed that in two of the three fatal reactions and five of the six near fatal reactions, the previous allergic event had not required urgent hospital intervention (**grade C**). Studies have also shown a significantly increased risk of near fatal and fatal reactions in patients with coexistent asthma. In one study, 13 of the 14 fatal or near fatal reactions occurred in patients with known asthma (7).

2.6 Adrenaline in pregnancy

Anaphylaxis is a relatively uncommon event in pregnancy that can have serious implications for both mother and fetus. Few cases of anaphylaxis during labour are described, particularly to antibiotics and to oxitocine (66). In some of these episodes, the use of IV adrenaline was essential for a good outcome either for fetus or mother. In other cases, the treatment used to resolve the episode was not reported (67).

The 2000 AAAAI Allergy Report (2000; 3: pag 127) "Special Consideration for Managing Anaphylactic/Anaphylactoid Reactions. *The Pregnant Patient"* shows the following conclusion on the treatment of anaphylaxis in pregnancy:

- Anaphylaxis is a risk situation for both mother and fetus
- Premature birth or abortion are not common complications of anaphylaxis
- Uterine cramps may be present in patients with anaphylaxis and may mime a premature labour or an abortion
- The use of parenteral (intravenous) epinephrine for the treatment of anaphylactic reactions during pregnancy is critical for a good outcome (**grade C**).

3. Self-injectable adrenaline

Anaphylaxis often occurs in the community in the absence of a health care professional. Prompt administration of self-injectable epinephrine as first-aid treatment in the context of a personalized emergency action plan is the key to survival (68).

Since 1995 self-injectable adrenaline is sold also in Italy and now it is dispensed to the patients who need it in the context of the National Health Service as a drug of H type (provided by the Hospitals to outside patients).

3.1 Introduction

Epidemiological data of anaphylaxis in the general population are sparse and influenced by definition, coding, and classification errors (69). So there is confusion about the prescription of adrenaline in the community.

The current opinion on prescription of auto-injectors is divided. Americans believe that all patients with an episode of major allergy should be prescribed an auto-injector (70). In the United Kingdom some people believe auto-injectors are over-prescribed (71).

In a review by McLean-Tooke (7), it appears that only 50-70% of patients prescribed auto-injectors for self administration of adenaline carry them around all times. Only 30-40% of these were able to correctly demonstrate how they would self-administer adrenaline A retrospective analysis showed that only 29% of children with recurrent anaphylaxis were treated with their adrenaline auto-injector. The subsequent need for adrenaline and hospital admissions were reduced in those patients who did received the appropriate dose by auto-injector (**grade C**) (7).

Adrenaline auto-injectors proved unsuccessful in nine of 14 patients with severe reactions, either due to unavailability (n=4), rapidity of reaction (n=1), incorrect dose (n=1), or despite the correct treatment (n=2) (**grade C**) (7). In another study, 23% of adult patients admitted that they would probably not be able to self administer adrenaline (one half would seek medical assistance and the other half would ask another person) (71).

Studies in primary and secondary care have shown that most doctors are themselves uncertain about the correct use of auto-injectors (72). Only instruction provided by an allergy specialist has been shown to have any effect on proper injection technique (**grade C**). In a recent study 100 GPs were inquired about diagnostic and therapeutic aspects of anaphylaxis. 36 to 46% gave correct answers to diagnostic questions. Only 14% were able to indicate the correct commercial name of the adrenaline auto-administration kit (73).

Patients need to be aware about expiry dates of their auto-injectors, although studies have shown that outdated auto-injectors still contain pharmacologically active and bioavailable adrenaline (74). Instruction by a physician familiar with auto-injectors and regular review of technique and reinforcement of the issues surrounding their use is therefore vital for these patients.

In another work, only 56% of the pediatricians were able to recognize either the problem of the food allergy or the treatment with adrenaline (75).

Further studies confirmed the poor compliance of patients to carry around the self-injectable adrenaline and to use it (76).

Studies of deaths caused by anaphylaxis, the worst-case scenario, might hold important lessons as to optimal treatment or at least indicate errors that can and should be avoided. For insect sting reactions, many of the fatalities occurred on the first reaction; however, in contrast, most fatal food-induced allergic reactions occurred in persons with a history of previous mild reactions and concomitant uncontrolled asthma (69). In the series of fatalities reviewed by Pumphrey (3), the median time from venom injection and food ingestion to cardiorespiratory arrest were 15 minutes (range, 4-120 minutes) and 30 minutes (range, 6-360 minutes), respectively. Epinephrine was not given to any of 32 victims of fatal stings and to 8 of 37 with fatal food allergy before arrest. In conclusion, risks for fatality include: concomitant asthma in patients with food allergy, and, poor asthma control, poor self-treatment, and no prophylactic treatment with immunotherapy in venom-induced anaphylaxis.

The American Academy of Allergy Asthma and Immunology recommends that all the patients, and particularly children, who experienced a real or suspected episode of anaphylaxis consult an allergologist in order to confirm the diagnosis, to identify the anaphylactic trigger , to educate the patient and to start desensitization when indicated (12).

3.2 Prescription of adrenaline (when)

In view of existing evidence of efficacy and of safety of self-injectable adrenaline and based on the observation that a prompt administration of adrenaline allows a better prognosis, any patient with a history of anaphylaxis should be prescribed self-injectable adrenaline.

Prescription of adrenaline seems to be eligible in the following situations:

- **patients with a previous anaphylactic episode according to the definition reported above (1.1) when the offending allergen cannot be avoided or identified (idiopathic anaphylaxis)**
- **patients with systemic cutaneous reactions (e.g. urticaria) when one or more risk factors are present as summarized at paragraph 1.5 (number 1 to 8).**

To prescribe self-injectable adrenaline correctly, the diagnosis of anaphylaxis must be well documented and related to an episode happened no more than two years before. Otherwise, the diagnosis must be accurately re-considered. In children food allergy can be outgrown although anaphylactic episodes during diagnostic re-challenge tests have been reported (77).

The correct prescription of adrenaline in adult patients fully diagnosed has to be planned life-long.

Patients (or their parents) prescribed injectable adrenaline are routinely evaluated on the first visit about their knowledge of how and when auto-injecting devices should be used.

According to International Guidelines, self-injectable adrenaline should be present and easily available and administered in school settings (78, 79), and also in public places such as airports, stations, schools, military settings, sport settings and so on (80). In some countries, the use of emergency therapies, including adrenaline, is recommended in the Dental Office (81).

3.3 Dosage

At the moment, there are only two fixed doses of adrenaline in auto-injectors:

- 330 mcg /0,30 ml (for adults or children > 50 Kg body weight)
- 165 mcg/0,30 ml (for children and people < 30 Kg body weight)

It is impossible to give a precise dose of 0.01 mg/kg to children weighing <15 kg by self- injectable adrenaline 0.15 mg, and children weighing between 15 and 30 kg using either the 0.15 mg or the 0.3 mg device. Physicians must therefore choose whether to underdose such children with the pediatric dose or to overdose them with the adult one (82).

In a child weighing 22.5 kg, an average weight for a 7-year-old child, the Jr formula delivers a 1.5-fold underdose and the adult dose delivers a 1.3-fold overdose.

The decision to use the adult dose rather than Jr one may be guided by the presence of 1 or more of the following criteria:

- Concurrent diagnosis of asthma
- Peanut, tree nut, milk, egg, fish or seafood anaphylaxis
- Poor access to emergency medical services, e.g. living or vacationing in a remote rural area
- Dysfunctional/chaotic family situation
- No reliable transportation available
- History of previous life-threatening reaction (note, however, that the absence of a history of life-threatening reaction does not rule out the possibility that such a reaction may occur in the future).

Lack of appropriate dose options should not deter them from recommending epinephrine for the first-aid, out-of-hospital treatment of anaphylaxis.

Some adolescents and adults may not be optimally treated with the maximum epinephrine dose of 0.3 mg available in an auto-injector. In addition, the 14.29 mm length needle on currently available auto-injectors may be too short to ensure intramuscular injection of epinephrine in obese individuals. In these cases, a second dose of adrenaline may be required (83).

A second dose of adrenaline should be prescribed in the following cases:

- Previous allergic reactions protracted or biphasic
- Previous severe or life-threatening allergic reactions
- Obesity
- Poor access to emergency medical services

We remember that in many foreign Countries, adrenaline is not available and is often very expensive (84-85).

3.4 Administration of adrenaline (how and why)

A proper treatment depends on:

1. availability of the drug in a convenient delivery system, such as Fastjekt (the only treatment present in Italy);
2. knowledge of indications of the drug;
3. technically accurate use of the device. Deficiencies in parental knowledge of indications, use of the auto-injector, and methodology of administration have been reported (7).

It is necessary to learn the correct use of adrenaline, asking the doctor; in fact, in case of reaction an high degree of anxiety either of the patients or of their caregivers, may cause an INCORRECT use of the drug (use directions inside the package should be carefully read).

How to use the self-injector:

1. Unscrew the cap off of the Fastjekt carrying case and remove the auto-injector from its storage tube.
2. Grasp unit with the black tip pointing downward.
3. Form fist around the unit (black tip down).
4. With the other hand, pull off the grey safety release.
5. Hold black tip near outer thigh.
6. Swing and **jab firmly** into outer thigh until it clicks so that unit is perpendicular (at a 90° angle) to the thigh (auto-injector is designed to work through clothing).
7. Hold **firmly against thigh** for approximately 10 seconds.
8. Remove unit from thigh and massage injection area for 10 seconds.
9. Call emergency phone numbers and seek immediate medical care (or go directly to a hospital).
10. Carefully place the used auto-injector (without bending the needle), needle-end first, into the storage tube of the carrying case that provides built-in needle protection after use. Then screw the cap of the storage tube back on completely, and take it with you to the hospital emergency room (do **NOT** remove until ready to use).
11. After injection, lye down possibly in Trendelmburg's position.

Note: Most of the drug (about 90%) remains in the auto-injector and cannot be reused. However the patient has received the correct dose of the medication.

For the best results the patients must be instructed to recognize the symptoms of anaphylaxis and to choose the correct time for the injection (86) as follows:

- **when the first symptoms of anaphylaxis appear, involving the skin and/or the respiratory tract (other symptoms involving other body systems may be present as well), after a contact with a known trigger, especially if far from home or from an emergency unit**
- **when the typical symptoms appear and rapidly worsen even if the triggering agent has not been recognized (contact with a "hidden allergen")**

3.5 Side effects

No side effect of self- injectable adrenaline are reported in literature. The only described side effect occurred after unintentional injection into a finger. (87) This may provoke severe pain due to potent vasoconstriction. The best therapy is the local infiltration with phentolamine, a well tolerated α-blocker.

3.6 Practical and psychological aspects (mainly in children)

The problem of anaphylaxis is particularly important in children with food allergy, who can experience this event in absence of parents or relatives, such as in a school setting. Food allergy and the potential for anaphylaxis is a significant problem that has no easy solution. Families must balance daily living with the constant threat of a potentially life-threatening exposure. Being prepared to face such an event requires acceptance that anaphylaxis might occur and taking acquaintance about how to administer treatment, including adrenaline (88, 89).
Parents of children with peanut allergy may experience significant disruption of their daily activities (90).
Proper education of patients, relatives and school staff in avoiding the offending agent, in recognizing the first signs of anaphylaxis and to achieve the correct treatment is particularly important (91). Training parents about the use of the self-injector is an important component to improving parental comfort in treating their child (92, 93).
All individuals known to be at risk for anaphylaxis should be equipped with accurate medical recordings listing their trigger factor(s), and relevant co-morbidities along with current medication. A viable options includes wallet cards and medical identification jewelry, with or without an embedded medical record. They must be correctly informed about the use of self-injectors and about the signs and symptoms of the anaphylactic attack.
Written indications, with simple non medical terms and proper brochures are recommended.
At the same time, patients must be instructed in using any other medication in the treatment of allergic symptoms, as antihistamines or anti-asthmatic drugs.
Patients are requested to show the doctors all the documents about their problems. They should also consult up

to date and reliable web sites, for instance, www.foodallergy.org.
Education of individuals with anaphylaxis and of their families and caregivers helps to avoid anxiety and fear and instills confidence in their ability to cope, not only by preventing anaphylaxis episodes, but also by recognizing and treating them promptly when they occur. All health care professionals, including physicians, nurses, emergency medical service technicians, and first responders need regular anaphylaxis education updates.
Patients with anaphylaxis might be first seen with serious and life-threatening symptoms. Evaluation and diagnosis, as well as long-term management, can be complex. The allergist-immunologist has the training and expertise to obtain a detailed allergy history, coordinate laboratory and allergy testing, evaluate the benefits and risks of therapeutic options, and counsel the patient on avoidance measures. For these reasons, patients with a history of anaphylaxis should be referred to an allergy-immunology specialist (49).
Because children spend a significant proportion of their day at school, pediatric emergencies such as exacerbations of medical conditions, behavioral crises, and accidental/intentional injuries are likely to occur. Recently, both the American Academy of Pediatrics and the American Heart Association have published guidelines that stress the need for school leaders to establish emergency-response plans to deal with life-threatening medical emergencies in children. The goals include developing an efficient and effective campus-wide communication system for each school with local Emergency Medical Services; establishing and practicing a medical emergency-response plan involving school nurses, physicians, athletic trainers, and the EMS system; identifying students at risk for life-threatening emergencies and ensuring the presence of individual emergency care plans; training staff and students in first aid and cardiopulmonary resuscitation (CPR); equipping the school for potential life-threatening emergencies; and implementing lay rescuer automated external defibrillator programs (94).
Although the potential for life-threatening allergic reactions in children is a significant health concern for schools, there is little information about circumstances surrounding anaphylactic events that occur in schools. Although not frequent, anaphylactic reactions are not uncommon events in schools. A systematic review of anaphylactic events that required epinephrine administration identified opportunities for improvement in the treatment of students with life-threatening allergies (95, 96).
In Italy, only recently the Minister of Public Health and Instruction issued guidelines to recognize persons involved in the administration of treatment in the school; treatments can be used if needed by the parents of the children with a written prescription from the doctor.
Recently, the EAACI Task Force on Anaphylaxis in Children concluded that there is an urgent need that each Country provides rules to define school responsibilities for administering education, and included anaphylaxis into emergency response programs for school staff. This will ultimately ensure a network of emergency response to anaphylaxis and the creation of an anaphylaxis surveillance system in schools (97).

Summary points

- **Anaphylaxis is a severe life threatening reaction that can affect all age groups**
- **The severity of previous reactions does not predict the severity of subsequent reactions**
- **Intramuscular adrenaline is the first line treatment for anaphylaxis, with intravenous adrenaline reserved for unresponsive anaphylaxis or circulatory collapse**
- **Early use of adrenaline in anaphylaxis is associated with improved outcomes**
- **Any patient with a systemic allergic reaction should be considered for an adrenaline auto-injeetor, depending on risk of further reactions**
- **There is a clear need to improve education of both patient and physician on the use and indications of adrenaline**

Appendix I

Self- injectable adrenaline in Hymenoptera venom allergy

Introduction

According to the available data on the natural history of Hymenoptera venom allergy in adults, a previous systemic reaction significantly increases the risk of a recurrence following a subsequent sting. However, this risk widely ranges from 20% to 75%, with regard to the patient's age, the severity of the previous reaction and the interval between the first and the subsequent reaction.
Risk factors for the severity of the resting reaction have been identified in older age, cardiovascular diseases, treat-

ment with beta-blocker drugs, insect type (honeybee and European hornet), mastcell disease (98-100).
Venom immunotherapy represents the only therapeutic treatment able to efficiently prevent the occurrence of a systemic sting reaction in sensitised subjects. The efficacy of venom immunotherapy (VIT) has been demonstrated in two controlled studies (Level of Evidence Ib) and in a subsequent wider number of prospective uncontrolled studies (63, 99).
Taking together all the prospective studies where VIT efficacy was evaluated by sting challenge, only 0.9% of *Vespid* venom allergic patients and about 20% of honeybee venom allergic subjects had a positive sting challenge, although the reaction was less severe than the pre-VIT reaction.
As for the duration of VIT, the studies which analysed reactions to a sting challenge one to three years after stopping VIT showed continued protection in the vast majority (83 to 100%) of cases with a relatively short period after stopping successful VIT of at least three years duration. Results were somewhat more favourable in *Vespula* than in bee-venom-allergic individuals, and in children as opposed to adults.
Some studies have analysed long-term protection up to 7 years after discontinuing VIT. Taken together these studies revealed relapses somewhat more frequently than the earlier studies with a shorter follow-up. Still, the vast majority - 80% -92%- remained protected when re -stung up to 7 years after VIT (63).
Through careful analysis of all these prospective studies a number of risk factors for the recurrence of a systemic reaction following Hymenoptera stings have been identified: insect type (honeybee), severity of reaction pre-VIT, systemic reaction during VIT, concomitant pathologies like mastocytosis and urticaria pigmentosa.
Systemic reaction: Systemic reactions due to Hymenoptera stings may induce a wide spectrum of symptoms ranging from urticaria to anaphylactic shock. Autoinjectable epinephrine should be prescribed for any type of systemic reaction, provided that allergic sensitisation has been demonstrated by skin testing and/or serum specific IgE antibodies. Patients should be advised to carry it with them at all times. In some patients it may be necessary to prescribe more than one kit of injectable epinephrine (like in the case of a previous biphasic or protracted reaction); the decision should be made case by case by the allergist
Large local reaction: After a large local sting reaction, between 5% and 15 % of patients will develop a systemic reaction when next stung. According to the vast majority of authors this risk is considered negligible; therefore the prescription of injectable epinephrine is unnecessary. However, it is optional and valuable case by case, in the presence of individual, environmental or occupational risk factors.
Systemic reaction with negative testing for venom specifici IgE: A low percentage of patients with a history of a previous systemic reaction shows negative test results for venom specific IgE antibodies. This may due to the long interval between the reaction and the testing (with the spontaneous disappearance of specific IgE), but also to the low sensitivity of the diagnostic methods. However, the absence of venom specific IgE antibodies does not mean that the clinical reactivity also disappears. An other possible explanation may be the presence of systemic mastocytosis or urticaria pigmentosa. Autoinjectable epinephrine should only be prescribed for severe systemic reactions; at the moment there is no consensus about the prescription of epinephrine in the case of mild systemic reactions, except for concomitant systemic mastocytosis or urticaria pigmentosa.
During venom specific immunotherapy: Although highly effective, VIT may not prevent a future reaction in a small percentage of patients. Risk factors for incomplete protection have been identified in honeybee allergy, concomitant systemic mastocytosis or urticaria pigmentosa. Autoinjectable epinephrine should always be prescribed until the standard protective maintenance dosage had been reached. Its prescription during the maintenance phase of VIT is a controversial question. Looking at the available data, autoinectable epinephrine should be prescribed in the following situations: severe pre-VIT systemic reaction, honeybee allergy, incomplete VIT protection, systemic reaction during VIT, concomitant systemic mastocytosis or urticaria pigmentosa.
After discontinuation of venom immunotherapy: Autoinjectable epinephrine should be prescribed case by case, keeping in mind the above-mentioned risk factors which are also risk factors for relapse after stopping VIT (63, 99).

Appendix II

Self-injectable adrenaline in food allergy

Introduction

The issue of assessing future risk of anaphylaxis is particularly confusing for food allergy (69).
In fact the severity of a previous reaction is a poor guide to symptoms during a future reaction: only 22% of pa-

tients with fatal food-induced anaphylaxis had a previous severe reaction (3).
Food allergy is by far the most important cause of anaphylaxis in children, followed by hymenoptera venom and drug allergy.
In recent population-based surveys of peanut, tree nut, and seafood allergy in the United States, considering only individuals who reported respiratory or multiple organ system reactions and making a generous assumption that 25% might have both seafood and peanut-nut allergy, about 1.5% of the general population could be at risk for anaphylaxis to these foods. (69)
Food anaphylaxis depends on different factors (101):
1. sensitization to a gastro-resistant allergen
2. sensitivity of the subject
3. dose of the ingested allergen
4. facilitating factors (alcohol, physical exercise, drugs, other foods)

There is no preventing therapy in case of food allergy, so diet must be very rigorous, fully avoiding the offending food also as "hidden allergen". "Hidden allergens" represent a very important risk factor and patients have to check carefully the food labels. The EU regulations exclude from labeling some foods, as freshly prepared foods, (102) but the most important reactions occurring when eating out in restaurants and cafes. Food allergic patients must be given correct and simple rules to follow when eating out. (103)

Prescription of self-injectable adrenaline

Patient with a well-documented food allergy, are very often eligible for self-injecting adrenaline:
- patients with previous anaphylaxis of any severity when the allergen cannot be easily avoided (this is very frequently the case for patients with food allergy)
- patients with diffuse skin reactions and/or pollen-fruit syndrome when one or more risk factors are present as summarized at paragrafh 1.5 (number 1 to 8)
- Patients allergic to thermo-and gastro-resistant allergens like Lipid Transfer Proteins or Seed Storage Proteins (104)

Appendix III

Self-injectable adrenaline in latex allergy

Latex-induced anaphylaxis can present in the operating room in patients, surgeons, nurses, or anesthesiologists (12). Latex has been reported to account for up to 17% of cases of intraoperative anaphylaxis. Latex-induced anaphylaxis might occur in a variety of situations, all involving direct contact with latex devices, usually gloves, or instruments or with aerosolization of latex antigen adhered to the cornstarch donning powder of latex gloves. Thus latex-induced reactions can occur with operative procedures when gloves are donned. Latex-induced reactions might occur immediately with latex contact or might be delayed up to 30 to 60 minutes. Intraoperative latex-induced anaphylaxis might be related to the administration of drug through a latex port before surgery or during the surgical procedure itself. Latex-induced reactions have also been reported to occur during dental procedures from latex glove or dams, during obstetric or gynecologic examinations, during latex condom use, and from blowing into rubber balloons. Patients with spina bifida are potentially at risk at each surgical procedure because of the numbers of procedures they undergo (105). It is important to recognize that cross-reactivity between latex and foods can occur. The most commonly reported cross-reactive foods include banana, avocado, kiwi, and chestnut (106).
In case of latex-fruit syndrome, the prescription of adrenaline is similar to the food allergy. In particular, self-injectable adrenaline must be prescribed in asthmatic patients allergic to latex , as they can show severe reactions in presence of latex as "hidden allergen" (107).

References

1. Sampson HA. Anaphylaxis and emergency treatment. Pediatrics 2003; 111: 1601-8.
2. Simons FE. First-aid treatment of anaphylaxis to food:focus on epinephrine. J Allergy Clin Immunol 2004; 113: 837-44.
3. Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000; 30: 1144-50.
4. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reaction to food. J Allergy Clin Immunol 2001; 107: 191-3.
5. Simons FE, Peterson S, Black CD. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. J Allergy Clin Immunol 2002; 110: 647-51.
6. Johnston SL, Unsworth J, Compels MM. Adrenaline given outside the context of life threatening allergic reactions. BMJ 2003; 326: 589-90.
7. McLean-TookeAP, Bethune CA, Fay AC, Spickett GP. Adrenaline in the treatment of anaphylaxis:what is the evidence? BMJ 2003; 327: 1332-5.
8. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms.J Allergy Clin Immunol 2002; 110: 341-8.

9. Kemp SF, Deshazo RD. Prevention and treatment of anaphylaxis. Clin Allergy ImmunoI 2004; 18: 729-54.
10. Calvari M, Cardinale F, Martello A, Muraro A, Pucci N, Savino F. Indicazioni alla prescrizione e somministrazione dell'adrenalina nel bambino affetto da anafilassi. Riv Immunol Allergol Ped 2005; 3: 11-9.
11. Sampson HA, Munoz-Furlong A, Campbell RL, et al. 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. J Allergy Clin Immunol 2006; 117: 391-7.
12. Lieberman P, Kemp SF, OppenheimerJ, Lang DM, Bernstein L, Nicklas RA. The diagnosis and management of anaphylaxis: An updated practice parameter. J Allergy Clin Immunol 2005; 115: S483-523.
13. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004; 114: 371-6.
14. Brown SG. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. Curr Opin Allergy Clin Immunol 2005; 5: 359-64.
15. Brown AF. Anaphylaxis gets the adrenaline going. Emerg Med J 2004; 21: 128-9.
16. Kemp SF, Lockey RF. Anaphylaxis: A review of causes and mechanisms. J Allergy Clin Immunol 2002; 110: 341-8.
17. Simons FE. Anaphylaxis, killer allergy: Long-term management in the community. J Allergy Clin Immunol 2006; 117: 367-77.
18. Sampson HA, Munoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol 2005; 115: 584-91.
19. Tang AW. A practical guide to anaphylaxis. Am Fam Physicians 2003; 68: 1325-32.
20. Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. Ann Allergy Asthma Immunol 2006; 97: 30-43.
21. Braganza SC, Acworth JP, Mackinnon DR, Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. Arch Dis Child 2006; 91: 159-63.
22. Ellis AK, Day GH. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation in 103 patients. Ann Allergy Asthma Immunol 2007; 98: 64-9.
23. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000; 106: 762-6.
24. Lieberman P. Biphasic anaphylactic reactions. Ann Allergy Asthma Immunol 2005; 95: 211-2.
25. Simon GA, Brown MB. Clinical features and severity grading of anaphylaxis. Ann Allergy Clin Immunol 2004; 114: 371-6.
26. Brown SG, Mullins RJ, Gold MS. Anaphylaxis: diagnosis and treatment. Med J Austr 2006; 185: 283-9.
27. .Yocum MW, Butterfield JH, Klein JS, et al. Epidemiology of anaphylaxis in Olmstead County: a population study. J Allergy Clin. Immunol 1999; 104: 452-6.
28. Boros CA, Kay D, Gold MS. Parent reported allergy and anaphylaxis in 4173 South Australian Children. J Paediatr Child Health 2000; 36: 36-40.
29. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States. An investigation into its epidemiology. Arch Intern Med 2001; 161: 15-21.
30. Clark S, Gaeta TJ, Kamarthi GS, Camargo CA. ICD-9-CM coding of emergency department visits for food and insect sting allergy. Ann Epidemiol 2006; 16: 696-700.
31. Peng MM, Jick H. A population-based study of the incidence, cause, and severity of anaphylaxis in United Kingdom. Arch Intern Med 2004; 164: 317-9.
32. Bohlke K, Davis RL, DeStefano F, et al. Epidemiology of anaphylaxis among children and adolescent enrolled in a health maintenance organization. J Allergy Clin Immunol 2004; 113: 536-42.
33. Moneret- Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening anaphylaxis: a review. Allergy 2005; 60: 443-51.
34. Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940,000 inhabitants of the Swiss Canton Bern. Clin Exp Allergy 2004; 34: 285-90.
35. Lieberman P, Camargo CA Jr, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy and 1mmunology Epidemiology of Anaphylaxis Working Group. Ann Allergy Asthma Immunol 2006; 97: 596-602.
36. Pastorello EA, Rivolta F, Bianchi M, Mauro M, Pravettoni V. Incidence of anaphylaxis in the emergency department of a general hospital in Milan. J Cromatogr B 2001; 756: 11-7.
37. Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: A review of 142 patients in a single year. J Allergy Clin Immunol 2001; 108: 861-6.
38. Simons FE, Chad ZH, Gold M. Anaphylaxis in children: real-time reporting from a national network. Allergy Clin Immunol Int J World Allergy Org 2004; (Suppl): 242-4.
39. Galimberti M, Maspoli M, Cadario G. La rete regionale di allergologia e l'Osservatorio per le gravi reazioni allelgiche. Not Allergologico 2002; 21: 206-9.
40. Maspoli M, Attisano C, Galimberti M. L'organizzazione in "Rete Regionale" dei servizi sanitari: l'esperienza della Regione Piemonte. Not Allergologico 2003; 22: 53-8.
41. Mullins RJ. Anaphylaxis: risk factor for recurrence. Clin Exp Allergy 2003; 23: 1033-40.
42. Pumphrey R. Anaphylaxis: can we tell who is at risk of a fatal reaction? Curr Opin Allergy Clin Immunol 2004; 4: 285-90.
43. Sampson HA. Peanut allergy. N Engl J Med 2002; 346: 1294-9.
44. Florian S, Kraut MT, Simonitsch-Krupp I, et al. Indolent systemic mastocytosis with elevated serum tryptase, absence of skin lesions, and recurrent severe anaphylactoid episodes. Int Arch Allergy Immunol 2005; 136: 273-80.
45. Laske N, Bunikowski R, Niggerman B. Extraordinarily high serum IgE and consequences for atopic phenotypes. Ann Allergy Asthma Immunol 2003; 91: 202-4.
46. Miller MM. Beta-blockers and anaphylaxis: are the risks overstated? J Allergy Clin Immunol 2005; 116: 933-4.
47. Cianferoni A, Novembre E, Pucci N, Lombardi E, Bernardini R, Vierucci A. Anaphylaxis: a 7-years follow-up survey of 46 children. Ann Allergy Asthma Immunol 2004; 92: 464-8.
48. Kemp A. Epipen epidemics. Reply. J Pediatr Child Health 2003; 40: 241-2
49. Lieberman P. Use of epinephrine in the treatment of anaphylaxis. Curr Op Allergy Clin Immunol 2003; 3: 313-8.
50. Greenberger PA. Epinephrine for anaphylaxis. Ann Allergy Asthma Immunol 2005; 94: 515-6.
51. Anchor J, Settipane RA. Appropriate use of epinephrine in anaphylaxis. Am J Emerg Med 2004; 22: 488-90.
52. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults:

intramuscular versus subcutaneous injection. J Allergy Clin Immunol 2001; 108: 871-3.
53. Song TT, Nelson MR, Chang JH, Engler RJ, Chowdbury BA. Adequacy of epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. Ann Allergy Asthma Immunol 2005; 94: 539-42.
54. Simons FE, Gu X, Johnston L, Simons KJ. Can epinephrine inhalations be substituted for epinephrine injection in children at risk for systemic anaphylaxis? Pediatrics 2000; 109: 720-3.
55. Rodrigo GJ, Nannini LJ. Comparison between nebulized adrenaline and beta-2 agonists for the treatment of acute asthma. A meta-analysis of randomized trials. Am J Emerg Med 2006; 24 (2): 217-22.
56. Portland M, Kerr D, Kelly AM. Adverse events associated with the use of intravenous epinephrine in emergency department patients presenting with severe asthma. Ann Emerg Med 2006; 47: 559-63.
57. Rawas-Qalaji MM, Simons FE. Sublingual epinephrine tablets versus intramuscular injection of epinephrine: Dose equivalence for potential treatment of anaphylaxis. J Allergy Clin Immunol 2006; 117: 398-403.
58. Brown SG, Blackman KE, Stenlake V, Heddle RJ. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. Emerg Med J 2004; 21: 149-15.
59. Lang DM. Anaphylactoid and anaphylactic reactions. Hazards of beta-blockers. Drug Saf 1995; 12: 299-304.
60. Goddet NS, Deschata A, Liberge O, et al. Paradoxical reaction to epinephrine induced by beta-blockers in anaphylactic shock induced by penicillin. Eur J Emerg Med 2006; 13: 358-60.
61. Vander Zanden J, Valuck B, Brunch C, et al. Systemic adverse effects of ophthalmic beta-blockers. Ann Pharmacother 2001; 35: 1633-7.
62. Muller U, Haeberli G. Use of beta-blockers during immunotherapy for hymenoptera venom allergy. J Allergy Clin Immunol 2005; 115: 606-9.
63. Bonifazi F, Jutel M, Bilo' MB, Birnbaum J, Muller U & the EAACI Interest Group of Insect Venom Hypersensitivity. Prevention and Treatment of Hymenoptera Venom Allergy: Guidelines for clinical practice. Allergy 2005; 60: 1459-70.
64. Thomas M, Crawford I. Best evidence topic report. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers. Emerg Med J 2005; 22: 272-3.
65. Pumphrey RSH. Fatal posture in anaphylactic shock. J Allergy Clin Immunol 2003; 112: 451-2.
66. Cabestrero D, Pèrez-Paredes C, Fernandez-Cid R, Arribas M. Bronchospasm and laryngeal stridor as an adverse effect of oxytocin treatment. Crit Care 2003; 7: 392-3.
67. Gei AF, Pacheco LD, Vanhook JW, Hankins GD. The use of continuous infusion of epinephrine for anaphylactic shock during labor. Obstet Gynecol 2004; 102: 1332-5.
68. Kemp A. Epipen use: good clinical practice. J Paediatr Child Health 2004; 40: 72-4.
69. Sicherer SH, Simons FE. Quandaries in prescribing an emergency action plan and self-injectable epinephrine for first- aid management of anaphylaxis in the community. J Allergy Clin Immunol 2005; 115: 575-83.
70. Ellis MD, Day JH. The role of epinephrine in the treatment of anaphylaxis. Curr Allergy Asthma Rep 2003; 3: 4-11.
71. Unsworth DJ. Adrenaline syringes are vastly over prescribed. Arch Dis Child 2001; 84: 410-1.
72. Hayman GR, Bansal JA, Bansal AS. Knowledge about using autoinjectable adrenaline: review of patients' case notes and interviews with general practitioners. Brit Med J 2003; 327: 1328-30.
73. Branco Ferreira M., Rodriguez Alves R. Are generaI practitioners alert to anaphylaxis diagnosis and treatment? Eur Annals Allergy Clin Immunol 2006; 38: 83-6.
74. Simons FER, Gu X, Simons KJ. Outdated EpiPen and EpiPen Jr autoinjectors: Past their prime? J Allergy Clin Immunol 2000; 105: 1025-30.
75. Krugman SD, Chiaramonte DR, Matsui EC. Diagnosis and management of food-induced anaphylaxis: a national survey of pediatricians. Pediatrics 2006; 118: 554-60.
76. Johnson TL, Parker AL. Rates of retrieval of self-injectable epinephrine prescriptions: a descriptive report. Ann AllergyAsthma Immunol 2006; 97: 694-7.
77. Barbi E, Gerarduzzi T, Longo G, Ventura A. Fatal allergy as a possible consequence of long-term elimination diet. Allergy 2004; 59: 668-9.
78. Murphy R. Administration of epinephrine for life-threatening allergic reactions in school settings. Pediatrics 2006; 117: 1862-9.
79. McIntyre CL, Sheetz AH, Carrol CR, Young MC. Administration of epinephrine for life-threatening allergic reactions in school settings. Pediatrics 2005; 116: 1134-40.
80. Haymore BR, Carr WW, Frank WT. Anaphylaxis and epinephrine prescribing patterns in a military hospital: underutilization of the intramuscular route. Allergy Asthma Proc 2005; 26: 361-5.
81. Hass DA. Management of medicaI emergencies in the dental office: Conditions in each country, the extent of treatment by the Dentist. Anesth Prog 2006; 53: 20-4.
82. Hayman GR, Bansal JA, Bansal AS. Knowledge about using autoinjectable adrenaline: review of patients' case notes and interviews with general practitioners. Brit Med J 2003; 327: 1328-30.
83. Kelso JM. A second dose of epinephrine for anaphylaxis: How often needed and how to carry. J Allergy Clin Immunol 2006; 117: 464-5.
84. Simons FE. Lack of worldwide availability of epinephrine autoinjectors for outpatients at risk of anaphylaxis. Ann Allergy Asthma Immunol 2005; 94: 534-8.
85. Fitzarris P, Empson M, Ameratunga R, et al. Anaphylaxis management: the essential role of adrenaline (epinephrine) autoinjectors. Should PHARMAC fund them in New Zealand? NZ Med J 2006; 5: 119-21.
86. Ewan PW, Clark AT. Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. Clin Exp Allergy 2005; 35: 751-6.
87. Velissariou I, Cottrell S, Berry K, Wilson B. Management of adrenaline (epinephrine) induced digital ischaemia in children after accidental injection from an EpiPen. Emerg Med J 2004; 21: 388.
88. Kim JS, Sinacore JM, Pongracic A. Parental use of EpiPen for children with food allergies. J Allergy Clin Immunol 2005; 116: 164-8.
89. Mandell D, Curtis R, Gold M, Hardie S. Anaphylaxis: how do you live with it? Health Soc Work 2005; 30: 325-35.
90. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol 2003; 14: 378-82.

91. Rosen JP. Empowering patients with a history of anaphylaxis to use an epinephrine autoinjector without fear. Ann Allergy Asthma Immunol 2006; 97: 418.
92. Walker S, Sheick A. Managing anaphylaxis: effective emergency and long term care are necessary. Clin Exp Allergy 2003; 33: 1015-9.
93. Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. J Allergy Clin Immunol 2006; 118: 699-704.
94. Hay GH, Harrer TB 3rd, Moore TG. Assessing the safety of severely food allergic children in school. J Sch Health 2006; 76: 479-81.
95. Patel MB, Bansaj PG, Tobin MC. Management of anaphylaxis in child care centers: evaluation 6 and 12 months after an intervention program. Ann Allergy Asthma Immunol 2006; 97: 813-5.
96. Murphy R. Administration of epinephrine for life-threatening allergic reactions in school settings. Pediatrics 2006; 117: 18629.
97. Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007; 857-71.
98. Bilò MB, Rueff F, Mosbech G, Bonifazi F, Oude-Elberink & EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. Allergy 2005; 60: 1339-49.
99. Bonifazi F, Bilò MB & AAITO Committee. Linee Guida AAITO sulla Diagnosi e Terapia della allergia a veleno di imenotteri. Eur Annals Allergy Clin Immunol 2004; S1: 1-24.
100. Moffit GE, Golden DBK, Reisman RE, et al. Stinging insect hypersensitivity: A Practice Parameter Update. J Allergy Clin Immunol 2004; 114: 869-86.
101. Asero R. Plant food allergies: diagnosis in clinical practice. Int ArchAllergy Immunol 2005; 138: 1-11.
102. Anadan C, Sheikh A. European developments in labelling allergenic foods. BMJ 2005; 331: 1156.
103. Perino A. in 'Allergia e Intolleranza Alimentare'; Capitolo 12, pag. 221-232. 2001 Pacini Editore.
104. Asero R, Mistrello G, Roncarolo D, e al. Immunological cross-reactivity between lipid transfer proteins from botanical unrelated plant-derived food: a clinical study. Allergy 2002; 57: 900-6.
105. Fiocchi A, Restani P, Ballabio C, et al. Severe anaphylaxis induced by latex as a contaminant of plastic balls in play pits. J Allergy Clin Immunol 2001; 108: 298-300.
106. Blanco C. Latex-fruit syndrome. Curr AllergyAsthma Rep 2003; 3: 47-53.
107. Beezhold DH, Reschke JE, Allen JH, Kostyal DA, Sussman GL. Latex protein: a hidden "food" allergen? Allergy Asthma Proc 2000; 21: 301-6.

EUR ANN ALLERGY CLIN IMMUNOL VOL 40, N 2, 53-60, 2008

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Eosinophilic esophagitis: from the case report to the evidence

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KEY WORDS

Eosinophilic esophagitis, Allergy, Pathogenesis, Epidemiology, Case report, Gastroesophageal reflux disease (GERD)

SUMMARY

Eosinophilic esophagitis (EE) is a rare disease characterized by esophageal symptoms and dense esophageal eosinophilic infiltrate, both of wich persist despite prolonged treatment with proton pump inhibitors. The pathogenesis is poorly understood, but there is an increasing body of clinical and basic evidence that EE is an immune-mediated disease triggered by both food and inhalant allergens. At present there is no consensus statement on the number of eosinophils required for the diagnosis, but generally a number of 20 eosinophils per high power field is considered a significant cut-off point. Therapies considered to be effective in the treatment of EE include: specific elimination diets or elemental diets; either systemic or topical corticosteroids therapy; and therapy with a selective inhibitor of leukotriene D4 receptor.

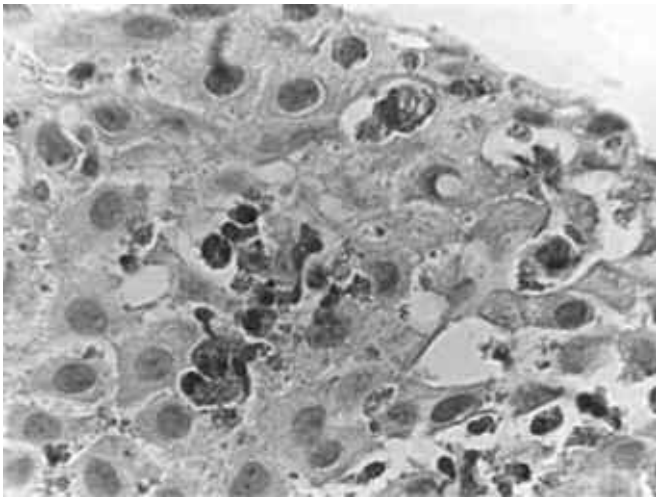
Case report

A 20-year-old woman presented to the emergency room of the Pordenone Hospital with a sensation of food impaction after meat ingestion. Over the prior 4 months she had experienced episodes of dysphagia unresponsive to acid-supressant treatment. Emergency upper gastrointestinal endoscopy revealed a small-caliber esophagus with concentric mucosal rings and the presence of meat bolus in the distal esophageal tract. It was difficult to pass the endoscope through, and resulted in a long and apparently superficial esophageal tear. The meat bolus was broken up with the diathermic loop and pushed into the esophagus. Biopsies were made of the proximal and distal esophageal mucosae. One hour after removing the obstruction, the patient manifested signs of pneumomediastinum, confirmed by the Computed Tomography, which showed a diffuse thickening of the esophageal wall with a small longitudinal tear.

The patient was hospitalized in the Surgery Department, where she recovered quickly and was discharged after ten days. Since the histological exam of the esophageal mucosae had revealed an intense eosinophilic infiltration [> 30 eosinophils (eos)/high power field (HPF)] with the presence of aggregates or microabscesses (aggregate of 4 or more contiguous eosinophils) (Fig. 1), the patient also was evaluated for allergies.

From the medical history it was clear that the patient, from age three to age eight, had suffered allergic bronchial asthma, with house dust mites hypersensitivity, for which subcutaneous immunotherapy had been started, but was suspended after a few months due to the appearance of significant adverse reactions. Subsequently, the patient presented only rhinitis, but for the last two years had been again experiencing dyspnoea, especially during the spring months. Moreover, for at least three years, she experienced oral allergic syndrome (OAS) after eating kiwi, apple, peach, cherry; and also

Figura 1 - Eosinophilic infiltration within esophageal squamous epithelium with the presence of aggregates or microabscesse (Magnification 400X)



had abdominal pains, and vomiting after ingesting walnuts and banana.

Skin prick tests (SPT) for aeroallergens showed hypersensitivity to *Graminaceae (4+), Compositae (4+), Plantago lanceolata (3+), Betulaceae (4+), Dermatophagoides pteronissinus (3+),* rabbit epithelium (3+) and cat epithelium (4+). The SPT for foods showed hypersensitivity to walnuts (3+), banana (3+) and kiwi (3+). All these hypersensitivities were confirmed by measuring the specific IgE (CAP-FEIA, Phadia, Sweeden).

After the diagnosis of eosinophilic esophagitis (EE) was done, the patient was placed on a diet free of the foods to which hypersensitivity had been shown, in addition to the fruit that resulted in OAS, and she was treated with methilprednisolone at the dosage of 1.5 mg/Kg/day divided into twice-daily doses for 3 weeks; then she was tapered off this medication over four weeks. At the end of the therapy with steroids, the patient was treated with montelukast 20 mg/day and over two months her digestive symptoms disappeared completely. After seven months from the first episode, she was submitted to a new endoscopic evaluation and the biopsies, conducted at various levels, confirmed the presence of a eosinophilic infiltration (15 eosinophils/HPF). The 24-hour esophageal pH monitoring was normal and the esophageal manometry testing showed normal esophageal motility.

The patient continued the treatment with montelukast for one year and then suspended this therapy. After the course of three years she remained asymptomatic.

The clinical case reported here represents a good paradigm of EE, for its clinical presentation, the co-presence of allergies, the histo-morphological characteristics, its complication, and its response to therapy. It provides, therefore, a valid introduction to a review of the most recent acquisitions relative to an emerging pathology, which has become an important and simulating field of interest for gastroenterologists and allergists alike.

Definition

EE as disease entity was first described in 1978 (1) and it is defined as a clinico-pathological disease characterized by esophageal symptoms and dense esophageal eosinophilic infiltration (> 20 eosinophils/HPF) both of which persist despite prolonged treatment with proton pump inhibitors (2). Furthermore it is important to exclude other disorders associated with similar clinical, histological, or endoscopic features, especially gastroesophageal reflux disease (GERD).

Epidemiology

The epidemiology of EE has not yet been well defined. At first considered very rare, in the last decade over 100 works have been published on this type of pathology and cases described world-wide include 1000 pediatric cases and 250 cases in adults (3).

It is unclear whether this represents heightened awareness and increased testing or a true escalation in incidence. To confirm the first hypothesis is the fact that, with greater awareness of the clinical and histopathological characteristics of this pathology, patients with multiple esophageal rings with intraepithelial eosinophils previously diagnosed as affected by GERD, but who didn't respond to standard acid suppression therapy, can now be classified as possible EE cases (3).

On the other hand, there is some evidence that demonstrates a true escalation in the disease incidence and prevalence. Noel et al. (4) reported a four-fold increase in prevalence among children from Ohio from 2000 to 2003. Straumann and Simon (5) prospectively followed adult patients with EE in Switzerland for a period of 15 years and reported a three-fold increase in the incidence of EE.

There are few epidemiological studies on EE, and they are not definitive, especially due to the absence of well-es-

tablished diagnostic criteria. Fox et al. (6) estimated that 6.8% of children with esophagitis had EE, while Liacouras et al. (7) reported EE in 3.4% of children with reflux symptoms.
Noel et al. (4) suggested in a pediatric population an incidence of 1 per 10,000 and a prevalence of 4.2 per 10,000 children. In adults, one report from Australia (8) identified EE in 19 patients from a population of 198,000 over a 21-month period. Recently, in a study conducted in Sweden on a random population-based sample of 1000 adults with or without esophageal symptoms the prevalence of EE was 0.1% (9).
EE appears to have a male predominance (about 2/3 of cases) both in children (10-13) and adults (8, 14-16) and occurs in all age groups. When EE affects adults, it is usually diagnosed in the third or fourth decade of life (8, 14).

Pathogenesis

The pathogenesis of EE is poorly understood, but there is an increasing body of clinical and basic evidence that EE is a disease related to an immune-mediated response triggered by exogenous allergens. Spergel et al. (13) found that 73% of EE patients had positive skin prick tests and 81% had positive patch tests (19% in patients with skin prick test negative). Recently, Sugnanam et al. (17) reported that younger patients with EE showed more IgE and patch sensitization to food, while older patients showed greater IgE sensitization to inhalant allergens. In the same study the prevalence of atopic eczema (55.6%), allergic rhinitis (93.3%) and asthma (66.7%) was significantly increased in the EE cohort as compared with the general Australian population.
If it is clear that there is an association between EE and other forms of atopic diseases, it is not well known as the antigen initiates the inflammatory response (3). There is some evidence that antigen exposure in the esophagus (i.e. foods) may serve as a trigger in some patients. The best support for this theory is that a number of patients will have symptomatic improvement when a food allergen is identified and then eliminated from the diet or when an amino acid-based formula is administred in children (12). On the other hand, there is evidence that antigens outside the esophagus (e.g. aeroallergens) can results in an immune reaction within the esophagus. Mishra et al. (18) developed a murine model of esophageal eosinophilia in which nasal and bronchial sensitization and challenge with the ubiquitous aeroallergen *Aspergillus fumigatus* led to esophageal but not gastric or small intestinal eosinophilia. In humans, there is often an historical and clinical association between environmental allergens and EE (19). Fogg et al. (20), in addition, reported a case of EE that occured in a patient affected by asthma and rhinoconjunctivitis with pollen hypersensitivity, which presented both symptomatic and histologic exacerbations of EE during high pollen season with resolution during winter months.
Other than the clinical correlation between EE and atopy, evidence is now being accumulated that EE is associated with TH-2 type immuno-response. In particular, increased levels of eosinophil-active TH-2 cytokynes (e.g. IL-4, IL-5, IL-13) as well as mast cells are present in the esophagus of patients with EE (21-23) and in addition, experimental models of EE can be induced in mice by means of overexpression of TH-2 cytokines (IL-5, IL-13) (18, 24).
IL-5 is a critical cytokine for differentiation and activation of eosinophils and likely plays a central role in trafficking eosinophils into the esophagus in patients with EE. Indeed, mice devoid of IL-5 or lacking the receptor for IL-5 have a significant reduction in gastrointestinal eosinophils, whereas overexpression of IL-5 can promote eosinophilic accumulation (25).
IL-13, a key mediator of eosinophilic inflammatory pathways, also seems to be important in the recruitment of eosinophils to the esophagus. Mishra et al. (26) and Blanchard et al. (27) demonstrated that direct delivery of murine or human IL-13 into the pulmonary tree induced esophageal eosinophilia, an effect that was blocked with antihuman IL-13 antibody (27). IL-13 induction of EE seems to be dependent on IL-5, eotaxin, and STAT-6 (26).
IL-4, also, has been implicated in eosinophilic accumulation, regulating trafficking and promoting adhesion to endothelium surfaces (28). Taken togheter, these studies support a role for TH-2 cytokines in the development of EE.
Finally, it has been recently found that the gene encoding eotaxin-3 is highly induced in patients with EE compared with its expression in healthy controls, and there is a single nucleotide polymorphism in the human eotaxin-3 gene associated with disease susceptibility (22). These results suggest that eotaxin-3 is not only an important molecule in the pathogenesis of EE, but that in EE patients there is an alteration in the gene that encodes eotaxin-3, thus implying a genetic susceptibility

for the development of EE, both in atopic and non-atopic patients (3).
Given that it is not possible to demonstrate a concomitant atopy in all patients with EE, however, it is interesting to report that which emerged from a recent study by Quaglietta et al. (29). Studying a group of 17 youth with EE, they found that 6 were affected by celiac disease, all of whom went into remission after following a gluten-free diet. In addition, a normalization in the eosinophilic count was reported. This association, in part unexpected since celiac disease, in contrast with EE, is a TH-1-type disease, requires additional confirmation and additional histochemical studies. If these associations are confirmed by further studies, it might be possible to conclude that, at least a subgroup of patients with EE and CD have the same initial pathological trigger event. Gluten, by immunological dysregulation, could stimulate both TH-1 and TH-2 reaction and be responsable for two different disorders, characterized by a common esophageal phenotype (29).

Clinical features

The clinical features and the presenting symptoms of EE may be different between children and adults. In children the predominant feature could be one of GERD-like symptoms including heartburn and regurgitation, nausea, vomiting, abdominal pain, dysphagia, and failure to thrive; food impaction is uncommon (11, 30). The characteristic symptoms of EE in adult patients is dysphagia, often accompanied by food impaction that may be the initial symptom. Dysphagia is often noted to be longstanding and resistant to management with acid-reducing medications (15,16,31). In most patients this likely represents a form of dysmotility given the absence of stricture. However, a subset of patients has obstructive symptoms related to strictures (6). In adults, although less common than in children, GERD-like symptoms were also reported (range, 7%–100%) as were chest pain (range, 1%–58%) and abdominal pain (range, 3%–25%). Diarrhea and weight loss were reported in some patients. Defining EE presents some problems because the presenting symptoms are similar to those of GERD. However, although GERD may coexist with EE, acid reflux is likely not important both in children and in adults with EE, and the symptoms and pathologic features intrinsic to EE do not respond to acid suppression treatment (32). The results of 24-hour esophageal pH monitoring are normal in > 90% of children (7) and in 85% to 100% of adults with EE (8, 15, 16). Although basal cell hyperplasia of esophageal mucosa often occurs in EE, as it does in GERD, the distinguishing primary histologic feature of EE is a striking eosinophilia of esophageal mucosa, often with eosinophil microabcesses.
As mentioned previously, the majority of patients with EE have a history of atopic conditions, such as asthma, allergic rhinitis, eczema, atopic dermatitis and food allergy. Recently, Sugnanam (17) demonstrated an age-specific sensitisation profile transition from food allergen sensitivity to inhalant allergen sensitivity as age increases in EE. Interestingly, the same Authors also reported an increased prevalence (10%) of anaphylaxis in the EE population.

Diagnosis

At present EE is diagnosed when suggestive symptoms and endoscopic features are supported by biopsy specimens demonstrating abnormal eosinophilic infiltration of the esophageal mucosa.

Endoscopic features

During endoscopic evaluation, several features characteristic of EE are found in the majority of patients. In one relatively large series (33) the most common endoscopic findings were, in order of frequency: mucosal transient or fixed rings (81%), vertical furrows (74%), strictures (31%), whitish nodules (15%), small calibre (10%) and oedema (8%). Fragile mucosa, or the so called "crèpe paper mucosa" is also found (34).
Esophageal rings have been reported as both radiographic and endoscopic findings in patients with dysphagia and seem to be correlated with the inflammatory process. Gupta et al. (35), indeed, found a high correlation between the endoscopic appearance of vertical lines and the presence of eosinophils on histological examination of esophageal biopsies.
Whitish exudates occurring in patches or distributed along the length of the esophagus (36,37) resemble mild superficial *Candida albicans* infection. Biopsies from these areas identify the histological correlate of the whitish area as eosinophils located superficially in the esophageal mucosa (6).
The mucosa of EE patients may be unusually fragile, with lesions appearing after minimal trauma. A characteristic feature is extensive longitudinal tears appearing after di-

latation of EE-mediated strictures, or merely the endoscopy itself (38).
Small-caliber esophagus represents another frequent endoscopic finding, and it is a complication of chronic inflammation associated with esophageal remodelling characterized by increased fibrosis, vascularity, vascular activation linked to eosinophil-derived TGF-β (39, 40, 41).
However, it is important to note that the above-mentioned extensive changes in esophagus structure occur in the absence of mucosal erosion or ulceration and it distinguishes EE from peptic disease.
Finally, it should be emphasised that EE may present with no or minimal macroscopic changes and that the endoscopic appearance is helpful but not diagnostic without a confirmatory biopsy. Therefore, all patients with endoscopic features of EE should have distal and proximal esophageal biopsies to confirm the EE diagnosis.

Histology

The esophagus is normally devoid of eosinophils (42, 43). Even if eosinophilic infiltration of the esophagus is found in other diseases (Tab. 1), it occurs at a lower density than in EE (< 10 eos/HPF). On the contrary, EE is characterized by a dense accumulation of eosinophils in the superficial layer of the esophageal wall and, in same cases, formation of eosinophilic microabscesses. However, the number of eosinophils required for diagnosis remains a matter of debate. Lee (44) was the first to empirically define "marked esophageal eosinophilia" as >10 eos/HPF demonstrated in at least two separate HPF. When Attwood and coworkers (31) reported their case series of EE as a "distinct clinicopathologic syndrome" they defined "high grade" EE as > 20 eos/HPF and "low grade" EE as ≤ 20 eos/HPF, but again this was an empiric definition. Since then, their serial study has frequently been used as justification for a diagnostic cut-off point of 20 eos/HPF.

Table 1 - Clinical conditions where esophageal eosinophil infiltrate is found but at lower density than EE (<20 eos/HPF)

- GERD
- Infection (parasitic, fungal)
- Myeloproliferative disorders
- Carcinomatosis
- Allergic vasculitis
- Autoimmune disorders (Sclerodermia)
- Recurrent vomiting
- Drugs

In a recent systematic review of the literature, Dellon et al (45) reported significant variability in diagnostic criteria for EE and concluded that, because of the lack of a common disease definition, conclusions drawn from the cumulative EE literature should be viewed with caution and that a consensus research-quality standard for diagnosis of EE is needed. Another critical point is that the area of an HPF may differ by microscope type from 0.12 to 0.44 mm^2. This is problematic, because eosinophil density (in eos/mm^2) can vary 23-fold when considered in the contest of the range of reported eosinophil count cut-off points (45). However in clinical practice, the diagnosis of EE can be made when suggestive symptoms and endoscopic findings are corroborated with a "significant" (putatively ≥ 20 eos/HPF) esophageal eosinophil infiltration on biopsy, even if, according to rigorous research methodology, such diagnostic imprecision is not acceptable (45).
Since eosinophil infiltration in the esophagus in EE cases may not be homogeneous [i.e, segmental, (46) patchy, (34) or even fluctuating (20)] multiple biopsy specimens from different levels of the esophagus are required. It is important, also, for the differential diagnosis with GERD where the eosinophilic infiltration (< 10 eosHPF) is present only on the distal esophagus.
Other histological features that are helpful but not essential for the diagnosis include basal zone hyperplasia, increased papillary size, and superficial layering of eosinophils with aggregates or microabscesses.

Treatment

As in diagnosis of EE, also for therapies there is no consensus. In general, the decision on the type of treatment to undertake is based on various factors, such as the age of the patient, the impact of the symptoms and of the treatment on the quality of life, and possible co-morbidity. Treatments determined to be successful in EE are nutritional treatment (specific elimination diet, elemental diets), systemic or topical corticosteroids, leukotriene receptor antagonist, and esophageal dilatation.
Furthermore, important differences in the clinical presentations of eosinophilic esophagitis in children and adults point toward the possible need for different treatment approaches in the two patient populations.

Nutritional treatment

The premise of an elimination diet is the hypothesis that food allergens are the stimulus for the inflammatory re-

sponse, particularly in the pediatric population. Kelly et al. (47) first reported that 10 children with EE documented long-term improvement in their symptoms with an amino acid-based elemental diet. Subsequent studies have confirmed the effectiveness of this intervention in larger groups of pediatric patients. Markowitz et al. (12), indeed, reported that 49 of 51 patients following an elemental diet showed significant improvement of symptoms within 8.5 days, and Spergel et al.(48) reported that, of 51 children with EE treated with an amino acid-based formula, all but two showed a clinical response. The Authors also demonstrate the utility of the atopy patch test (APT) in addition to the SPT to identify potential allergenic foods. In the largest series to date, Liacouras et al. (49) in a retrospective study reported their findings on 381 patients. Dietary restriction or complete dietary elimination using an amino acid-based formula significantly improved both the clinical symptoms and esophageal histology in 75 and 172 patients, respectively.

There are few data available regarding the efficacy of dietary restrictions in adults. Straumann et al. (14) in a preliminary trial including six adult patients with active EE sensitized to several foods, reported that the elimination diet failed to reduce disease activity.

Nutritional treatments, therefore, seem to be more efficacious in children, where close collaboration between the pediatrician and allergist is essential to identify the presence of potentially allergenic foods. However, in some cases an elemental diet formula is required to induce a remission. A later reintroduction of foods must take into account the results of SPT, APT, and possible measures of specific IgE. Additional studies are needed in adults with the end of establishing the role of the diet in improving symptoms and in reducing eosinophilic infiltration.

Corticosteroids

Corticosteroids, either systemic or topical, have proven to be effective in the treatment of EE.

Liacouras et al. (7) studied a population of 20 children with EE (mean age, 5.8 years). Thirteen patients became asymptomatic and 6 showed marked improvement after a 4-week treatment period of methylprednisolone 1.5 mg/kg/twice daily. At follow-up biopsy, the number of eosinophils per HPF decreased from 34.2 to 1.5. After 12 months,10 patients required a second course of systemic steroid treatment. Because repeated courses of systemic corticosteroids are associated with an increased risk of adverse effects, some investigators have assessed the efficacy of topical steroids in EE. Faubion et al. (50) treated 4 boys (age 12-13 years) with EE (> 50 eos/HPF) by swallowed fluticasone (220 μg, one puff four times daily). The treatment was given by an inhaler without a spacer and the patients were instructed to swallow after inhalation. The therapy induced a resolution of symptoms within a week. Teitelbaum et al. (11) used fluticasone propionate with marked improvement in symptoms and disappearance of eosinophilic infiltration in the esophagus, as well as of the number of CD3+ and CD8+ cells, in 11 children with EE. The only side effect was esophageal candidiasis (2 patients). Arora et al. (16) evaluated swallowed fluticasone in adults who had had solid food dysphagia for at least 6 years. Therapy for 6 weeks resulted in complete dysphagia relief for a minimum of 4 months. There were no cases of candidiasis and the only adverse effect was a transient dry mouth. Three patients had a relapse of dysphagia after 4 months and they responded well to a repeat topical corticosteroid treatment. Recently, a group of investigators (51) presented their experience with a topical corticosteroid specifically designed for use in EE: topical viscous budesonide (budesonide mixed with sucralose). This suspension may be used in younger or neurologically impaired children who are not able to perform an inhaler puff-and-swallow sequence. They used doses of 1-2 mg per day in 14 pediatric patients with EE. Histologic improvement was documented in 86% of patients following 3-4 months of therapy.

The efficacy of topical versus systemic corticosteroids has been evaluated in a controlled trial in pediatric patients (52). All 20 patients in the prednisone group were asymptomatic at the end of the treatment period compared with 19 of the 22 patients who received fluticasone, implying a slightly better efficacy for prednisone. However, twenty weeks after patients stopped therapy, there was similar relapse (35%) in the two groups. These data suggest that it is preferential to use topical corticosteroid in an attempt to limit side effects.

Leukotriene Receptor Antagonist

Attwood et al. (15) treated eight patients with Montelukast, a selective inhibitor of the leukotriene D4 receptor, at a starting dose of 10 mg/day that was increased if required up to a total of 100 mg daily. They found that 88% of EE patients had complete resolution of their symptoms. Once symptoms relief had been achieved the dose was then reduced to maintenance levels (20-40 mg/day). The patients continued the treatment for 14

months and no relapse of symptoms has been described while continuing the medication but six patients had recurrence within three weeks of cessation or reduction in medication. Intrerestingly, the treatment with Montelukast for more than four months did not change the density of eosinophils, but by blocking the D4 receptor the inflammatory action of these cells is reduced. Therefore, the use of leukotriene receptor antagonist in EE is promising, but needs evaluation in larger controlled studies, to define also the appropriate dosing schedule and the duration of treatment.

Esophageal dilatation

Esophageal strictures in EE are responsive to dilatation (53). However, because of potential risks of esophageal tearing and perforation, dilatation should be performed only in patients who fail medical therapy and have severe dysphagia. Langdon et al. (54, 55) suggests that dilatation proceed with great caution and recommends inspection of the esophagus after the passage of each dilator.

Future directions in EE therapy

As mentioned above, basic evidence supports the role of IL-5 in the eosinophilic infiltration of the esophagus. The effects of anti-IL-5 treatment using mepolizimab, a humanized blocking antibody against IL-5, have been reported in patients with various hypereosinophilic syndromes, including an 18-year-old man with severe EE, who had been unresponsive to an elimination diet, topical fluticasone, and systemic prednisone (56). After 3 administrations of i.v. mepolizumab (10 mg/kg at 4-week intervals) he presented a marked symptomatic and endoscopic improvement, as well as a >10-fold decrease in esophageal eosinophilic infiltration. However, larger multicenter studies will be needed to address both efficacy and safety concerns before general acceptance of this treatment regimen.
Theoretically, anti-IL-13 and anti-eotaxin-3 monoclonal antibody may be the target for future research strategy in the treatment of EE, but at present there is no experimental evidence of their use.

References

1. Landres RT, Kuster GG, Strum WB. Eosinophilic esophagitis in a patient with vigorous achalasia. Gastroenterology 1978; 74: 1298-301.
2. Furuta GT, Straumann A. The pathogenesis and management of eosinophilic esophagitis. Aliment Pharmacol Ther 2006; 24: 173-82.
3. Ferguson DD, Foxx-Orenstein. Eosinophilic esophagitis: an update. Dis Esophagus 2007; 20: 2-8.
4. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis: N Engl J Med 2004; 351: 940-1
5. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? J Allergy Clin Immunol 2005; 115: 418-9.
6. Fox VL, Nurko S, Furuta GT. Eosinophilic esophagitis: it's not just kid's stuff. Gastrointest Endosc 2002; 56: 260-70.
7. Liacouras CA, Wenner WL, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. J Pediatric Gastroenterol Nutr 1998; 26: 380-5.
8. Croese J, Fairley SK, Masson JW, Chong AK, Whitaker DA, Kanowski PA, Walker NI. Clinical and endoscopic features of eosinophilic esophagitis in adults. Gastrointest Endosc 2003; 58: 516-22
9. Ronkainen J, Talley NJ, Aro P, Storskrubb T, Johansson SE, Lind T, et al. Prevalence of oesophageal and eosinophilic oesophagitis in adults: the population-based Kalixanda study. Gut 2007; 56: 615-20.
10. Cheung KM, Oliver MR, Cameron DJ, Catto-Smith AG, Chow CW. Esophageal eosinophilia in children with dysphagia. J Ped Gastroenterol Nutr 2003; 37: 498-503.
11. Teitelbaum JE, Fox VL, Twarog FJ, Nurko S, Antonioli D, Gleich G, et al. Eosinophilic esophagitis in children: Immunopathological analysis and response to fluticasone propionate. Gastroenterology 2002; 122: 1216-25.
12. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003; 98: 777-82.
13. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and path tests to identify causative foods in eosinophilc esophagitis. J Allergy Clin Immunol 2002; 109: 363-8.
14. Straumann A, Spichtin HP, Grize L, Buchen KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003; 125: 1660-9.
15. Attwood SEA, Lewis CJ, Bronder CS, Morris CD, Armstrong GR, Whittam J. Eosinophilic oesophagitis: a novel tratment using Montelukast. Gut 2003; 52: 181-5.
16. Arora AS, Perrault J, Smirk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. Mayo Clin Proc 2003; 78: 830-5.
17. Sugnanan KKN, Collins JT, Smith PK, Connor F, Lewindon P, Cleghorn G, Withers. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. Allergy 2007; 62: 1257-60.
18. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergen and eosinophils in experimental esophagitis. J Clin Invest 2001; 107: 83-90.
19. Simon D, Marti H, Heer P, Simon HU, Braathen LR, Straumann A. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airways diseases. J Allergy Clin Immunol 2005; 115: 1090-2.
20. Fogg MI, Richelli E, Spergel JM. Pollen and eosinophilic esophagitis. J Allergy Clin Immunol 2003; 112: 796-7.

21. Walsh SV, Antonioli DA, Goldman H, Fox VL, Bousvaros A, Leichtner AM, Furuta GT. Allergic esophagitis in children: a clinicopathological entity. Am J Surg Pathol 1999; 23: 390-6.
22. Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, et al. Eotaxin-3 and uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Invest 2006; 116: 536-47.
23. Straumann A, Bauer M, Fisher B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with T(H)2-type allergic response. J Allergy Clin Immunol 2001; 108: 954-61.
24. Mishra A, Hogan SP, Brandt, Rothenberg ME. IL-5 prototes eosinophilic trafficking to esophagus. J Immunol 2002; 168: 2464-9.
25. Rothenberg ME, Mishra A, Brandt EB, Hogan SP. Gastrointestinal eosinophils. Immunol Rev 2001; 179: 139-55.
26. Mishra A, Rothenberg ME. Intratracheal IL-13 indices eosinophilic esophagitis by IL-5, eotaxin-1, and STAT 6-dependent mechanism. Gastroenterology 2003; 125: 1419-27.
27. Blanchard C, Mishra A, Saito-Akei H, Monk P, Anderson I, Rothenberg ME. Inhibition of human interleukin-13-induced respiratory and oesophageal inflammation by anti-human-interleukin-13 antibody (CAT-354). Clin Exp Allergy 2005; 35: 1096-103.
28. Yan BM, Shaffer EA. Eosinophilic esophagitis: a newly established cause of dysphagia. World J Gastroenterol 2006; 21: 2328-34.
29. Quaglietta L, Coccorullo P, Miele E, Pascarella F, Troncone R, Staiano A. Eosinophilic oesophagitis and coeliac disease: is there an association? Aliment Pharmacol Ther 2007; 26: 487-93.
30. Orenstein SR, Shalaby TM, Di Lorenzo C, Putnam PE, Sigurdsson L, Mousa H, Kocoshis SA. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. Am J Gastroenterol 2000; 96: 1422-30.
31. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993; 38: 109-16.
32. Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? Clin Gastroenterol Hepatol 2004; 2: 523-30.
33. Gonsalves N, Kahrilas P, Hirano I. Eosinophilic esophagitis (EE) in adults: emerging entity or misdiagnosed malady. Gastrointest Endosc 2005; 61: AB132.
34. Straumann A, Rossi L, Simon HU, Heer P, Spichtin HP, Beglinger C. Fragility of the esophageal mucosa: a pathognomonic endoscopy sign of primary eosinophilic esophagitis. Gastrointest Endosc 2003; 57: 407-12.
35. Gupta SK, Fitzgerald JF, Chong SK, Croffie JM, Collins MH. Vertical lines in distal esophageal mucosa (VLEM): a true endoscopic manifestation of esophagitis in children? Gastrointest Endosc 1997; 45: 485-9.
36. Ahmed A, Matsui S, Soetikno R. A novel endoscopic appearance of idiopathic eosinophilic esophagitis [letter]. Endoscopy 2000, 32: S33.
37. Furuta GT. Clinicopathologic features of esophagitis in children. Gastrointest Endosc Clin NA. 2001; 11: 683-715.
38. Nielsen RG, Husby S. Eosinophilic oesopagitis: epidemiology, clinical aspects, and association to allergy. J Ped Gastroenterol Nutr 2007; 45: 281-9.
39. Gharacee- Kermani M, McGarry B, Lukas N, Huffnagle G, Egan RW, Phan SH. The role of IL-5 in bleomycin-induced pulmoray fibrosis. J Lekoc Biol 1998; 64: 657-66.
40. Phipps S, Ying, Wangoo A, Ong YE, Levi-Schaffer F, Kay AB. The relationship between allergen-induced tissue eosinophilia and markers of repair and remodeling in human atopic skin. J Immunol 2002; 169: 4604-12.
41. Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. J Allegy Clin Immunol 2007; 119: 203-12.
42. Shub MD, Ulshen MH, Hargrove CB, Siegal GP, Groben PA, Askin FB. Esophagitis: a frequent consequence of gastroesophageal reflux in infancy. J Pediatr 1985; 107: 881-4.
43. Black DD, Haggitt RC, Orenstein SR, Whitington PF. Esophagitis in infants. Morphometric histological diagnosis and correlation with measures of gastroesophageal reflux. Gastroenterology 1990; 98: 1408-14.
44. Lee RG. Marked eosinophilia in esophageal mucosal biopsies. Am J Surg Pathol 1985; 9: 475-9.
45. Dellon ES, Aderoju A, Woosley J, Sander RS, Shahenn NJ. Variability in diagnostic criteria for eosinophilic esophagitis: a systematic review. Am J Gastroenterol 2007; 102: 1-14.
46. Liacouras CA. Eosinophilic esophagitis in children and adults. J Pediatr Gastroenterol Nutr 2003; 37 suppl 1: S23-28.
47. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology 1995; 109: 1503-12.
48. Spergel JM, Brown-Whitehorn. The use of pacth testing in the diagnosis of food allergy: Curr Allergy Asthma Rep 2005; 5: 86-90.
49. Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E, et al. Eosinophilic esophagitis: a 10 year experience in 381 children. Clin Gastroenterol Hepatol 2005; 3: 1198-206.
50. Faubion WA, Perrault J, Burgart LJ, Zein NN, Clawson M, Freese DK. Treatment of eosinophilic esophagitis with inhalated corticosteroids. J Pediatr Gastroenterol Nutr 1998; 27: 90-3.
51. Aceves SS, Dohil R, Newbury RO, Bastian JF. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. J Allergy Clin Immunol 2005; 116: 705-6.
52. Gupta S, Fitzgerald J, Davis M. Treatment of allergic eosinophilic esophagitis with oral prednisone and swallowed fluticasone: a randomized, prospective study in children. Gastroenterology 2003; 124: A-19.
53. Feczko P, Halpert R, Zonca M. Radiographic abnormalities in eosinophilic esophagitis. Gastrointest Radiol 1985; 10: 321-4.
54. Langdon DE Corrugated ringed esophagus[letter]. Am J Gastroenterol 1993; 88: 1461.
55. Langdon DE. Corrugated ringed and too small esophagi. Am J Gastroenterol 1999; 94: 542-3.
56. Garrett JK, Jameson SC, Thomson B, Collins, Wagoner LE, Freese DK, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndrome. J Allergy Clin Immunol 2004; 113: 115-9.

Eur Ann Allergy Clin Immunol Vol 40, N 2, 61-63, 2008

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The wasp-horsefly syndrome

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Key words

Horsefly, Diptera bites, Hymenoptera allergy

Summary

Here are two cases of two male patients of 57 and 62 years of age, already known as allergic to stinging hymenoptera venom, who after a horsefly bite have presented a serious 3-4 degree-type Mueller classification systemic reaction. The diagnosis has been carried out clinically and after an accurate environmental anamnesis and along with prick tests and RAST, further specific entomological confirm. In literature the so called wasp-mosquito-syndrome has been indicated where hyaluronidase has been referred to as the cross allergen, between the hymenoptera venom and the mosquito saliva, which likely triggers the reaction. We believe that it is also possible to take into consideration a wasp-horsefly-syndrome as well, supposing the increased risk of anaphylactic reactions to Tabanidae bites, relatively frequent in areas with animals and streams, in subjects sensitized to stinging hymenoptera. We also suggest the possibility that in these subjects some systemic reactions are due in fact to Tabanidae bites and not so much for the failure of a possible active ITS of stinging hymenoptera.

Introduction

In literature several are the indications telling us that in subjects sensitive to hymenoptera bites there is a high risk of triggering systemic reactions, up to anaphylaxis(1, 2) after the bite of some blood sucking diptera and in particular *mosquitoes* (*Aedes c.*).

Therefore the so called wasp-mosquito syndrome has become relevant and a detailed analysis has indicated hyaluronidase as the cross allergen between the hymenoptera venom and the diptera saliva which likely triggers the reaction. It is not clear if this syndrome involves exclusively *mosquitoes* or it can also be considered for other Diptera families such as *Tabanidae* (3, 4) which can be responsible for systemic reactions. We have recently published an article about the case of a subject sensitive to hymenoptera with a 2-3 degree Mueller reaction who had also suffered from an anaphylactic reaction after a Hippobosca equine (horsefly), a Diptera of the superfamily of the *Hippoboscoidea*, present in our rural areas and near horses (5).

Therefore we believe it is of interest to report our clinical experiences concerning two patients allergic to hymenoptera who have suffered from an anaphylactic reaction to both insect species (*vespula* and *tabanidae*).

We believe that along with a wasp-mosquito syndrome it is also possible to take into consideration a wasp-horsefly syndrome agreeing with what has been presented by Freye and Litwin (6) who have supposed a higher risk of anaphylactic reactions to Diptera bites, relatively frequent, in subjects sensitized to hymenoptera.

Case reports

Clinical case 1

A 57-year-old male, with a positive anamnesis to hymenoptera venom sensitization for a previous urticaria with dyspnea, dysphonia and hypotension after a *Vespula sp*. sting, was bitten on the neck by an unidentified insect described as of a grey colour and with a lengthened body. Just after a few minutes the patient manifested angioedema of face and general urticaria, feet and tongue paraesthesias with a temporary loss of consciousness. He was successfully treated by the ER, where he remained under observation until the next day when he was dismissed. The insect was killed and later kept by our patient, it was identified as a horsefly (*Haematopa pluvialis*) giving us further evidence to the lack of responsibility by the hymenoptera role as the anaphylaxis trigger factor.

Clinical case 2

A 62-year-old patient suffering from hypertension and allergic to hymenoptera venom with a previous Mueller 3-type reaction, under treatment with specific immunotheraphy of *Vespula sp* venom (ITS). While being outside near some grazing cattle, he was bitten on the arm by a yellow or green insect, very much like a wasp. He showed pain on the bite site with a slight blood drip and after 5' a general urticaria appeared with initial dyspnea and loss of consciousness, so serious as to use adrenaline. About 6 months later he was bitten again and presented the same symptoms but this time he was able to capture the insect and we found out, surprisingly enough, that it was not a *Vespula*, which from the description could have easily been, but a horsefly, the *Chrisops sp*., which looks very similar to hymenoptera and it is very common in rural areas near streams and animals.

Materials and methods

Live Test

For the diagnosis we have performed intracutaneous tests with hymenoptera venom available on the market (Pahrmalgen, Alk Abellò) and prick tests for Diptera (Stallergens) with a mix of *Aedes c*. and *Tabanidea* whole body. The test with readings after about 15-20 minutes was considered positive with the result of a ≥ 5 mm pomphus along with erythema. Histamine at 1% and human

Table 1 *- Diptera* classification

Order	Sub-order	Division	Superfamily	Family	Species
Diptera	Nematocera	Tipulomorpha	Tipuloidea	Tipulidae	*Stipula sp*
		Culicomorpha	Culicoidea	Simulidae	*Simulium d.*
	Brachycera	Ortorrapha	Tabanoidea	Tabanidae	*Crysops sp*
					Tabanus sp
					Hematopota pluvialis.
		Cyclorrapha	Asiloidea	Asilidae	*Laphria sp*
			Tephritoidea	Tephritoidar	*Anastrepha fraterculus*
			Drosophiloidea	Drosophiloidae	*Drosophila melanor*
					Drosophila suboscura
			Hippoboscoidea	Glossinidae	*Glossina morsitans*
					Glossina palpalis
				Hippoboscidae	*Ornihomia avicularia*
					Liptotena cervi
					Ornithoica vicina
					Hippobosca equina

albumin have been used as respectively positive and negative control.

In-vitro Test

The total and specific IgE dosage for hymenoptera and diptera venom on a serum sample has been carried out with the CAP system by Pharmacia, following the instructions included in the kit.

Discussion

In the two reported cases the diagnosis has been carried out clinically and after an accurate environmental anamnesis with a further specific entomological confirm, with skin prick-tests with *Tabanidae* sp. whole body resulted positive and with RAST which resulted positive in the second patient (5.4 U/ml) for *Tabanidae* sp.
For the time being lacking a purified allergen extracted from diptera salivary gland (7) we have no diagnostic reliability apart from the clinical one. Up to now all available data is the one between mosquito and wasp, reported by Sabbah, which shows to the electrophoresis a protein common to both extracts of 44kD, similar to the hyaluronidase. The author also supposes the possibility of a cross-reaction also in *Tabanidae* (4). Since blood sucking diptera taxonomy is quite complex (8) and each species is peculiar to area, environment and seasonal distribution and to all different saliva compositions (9), it will be fundamental to go deeper into our knowledge. These two cases increase the number of this type of reports and give support to the suspect that, due to the wide diffusion of Diptera(10), some systemic reactions must be due in fact to *Tabanida*e bites (11) and/or *Hippoboscidae* (5) and not so much as an ITS failure. To enlighten this concept it is therefore fundamental to improve our knowledge as for *brachycera-diptera* taxonomy (Tab. 1) which is extremely complex and also to go deeper in our studies aiming at the identification of cross-reaction antigenes between Diptera and Hymenoptera as to implement a specific immunotherapy able to protect people even from horseflies and *Hippobosca equina*.

References

1. Mc Cormack DR, Salata KF, Hershey JN, Carpenter GB, Engler PJ. Mosquito bite anaphylaxis: immunotherapy with whole body extracts. Ann Allergy Asthma Immunol 1995; 74 (1): 39-44.
2. Peng Z, Beckett AN, Engler RJ, Hoffman DR, Ott NL, Simons FE. Immune responses to mosquito saliva in 14 individuals with acute systemic allergic reactions to mosquito bites. J Allergy Clin Immunol 2004
3. Sabbah A, Hassoun S, Drouet M, Lauret MG, Doucet M. The wasp-mosquito syndrome. Allerg Immunol (Paris) 1999; 31 (6): 175-84.
4. Sabbah A, Hassoum S, Drouet M, Lauret MG, Doucet M. The wasp-mosquito syndrome: extension of cross-allergenicity to the horsefly. Allerg Immunol (Paris) 2000; 32 (1): 16-9.
5. Quercia O, Emiliani F, Foschi GF, Stefanini GF. Anaphylactic reaction after Hyppobosca equina bite. Alergol Immunol Clin 2005; 20: 31-3.
6. Freye HB, Litwin C. Coexistent anaphylaxis to Diptera and Hymenoptera. Ann Allergy Asthma Immunol 1996; 76 (3): 270-2.
7. Hemmer W, Focke M, Vieluf D, Berg-Drewniok B, Gotz M, Jarisch R. Anaphylaxis induced by horsefly bites: identification of a 69 kd IgE-binding salivary gland protein from Chrysops spp. (Diptera, Tabanidae) by western blot analysis. J Allergy Clin Immunol. 1998; 101: 134-6.
8. Nirmala X, Hypvsa V, Zurovec M. Molecular phylogeny of Calyptratae (Diptera: Brachicera): the evolution of 18S and 16S ribosomial rDNAs in higher dipterans and their ude in phylogenetic inference. Insect Molec Biol 2001; 10 (5): 475-85.
9. Kazimirova M, Sulanova M, Kozanek M, Takac P, Labuda M, Nuttall PA. Identification of anticoagulant activities in salivary gland extracts of four horsefly species (Diptera, tabanidae). Haemostasis 2001; 31 (3-6): 294-305.
10. Frazier CA. Biting insects. Arch Dermatol 1973; 107: 400-2.
11. De Maat-Bleeker F, van Bronswijk EMH. Allergic reaction caused by bites from blood-sucking insects of the Tabanidae family, species Haematopota pluvialis (L). Allergy 1995; 50: 388.

News

Joint statement on FDA investigation of Singulair from the ACAAI and AAAAI

ARLINGTON HEIGHTS, IL - Leadership from the American College of Allergy, Asthma & Immunology and the American Academy of Allergy Asthma & Immunology today released the following statement in response to the Thursday announcement of a Food and Drug Administration investigation into Singulair:

There are no data from well-designed studies to indicate a link between Singulair and suicide. The concern expressed by the FDA is based entirely on case reports and there is no indication that such effects apply to other leukotriene-modifying medications.

Post-marketing case reports are incomplete. Furthermore, comparative data are lacking on the incidence of suicide in the general population versus the incidence in patients taking Singulair. Thus, it is unknown whether there is an increased incidence of suicide in patients receiving Singulair.

Based on the information currently available, patients taking Singulair should continue to take the medication as prescribed provided: 1) the patient and physician feel the medication is effective; and 2) the patient does not experience any suicidal behavior or thoughts.

Patients who experience suicidal thoughts or demonstrate suicidal behavior should consult their physician immediately to discuss whether to continue with this medication. Patients should not hesitate to consult their physician if they feel uncomfortable continuing on the medication.

American Academy of Allergy Asthma & Immunology (AAAAI) - For immediate release, December 19, 2007

Menopausal women may have an increased asthma risk, from the*Journal of Allergy and Clinical Immunology*.

MILWAUKEE-Menopause is associated with lower lung function and more respiratory symptoms, especially among lean women, according to a new study in the *Journal of Allergy and Clinical Immunology* (JACI).

The study, "Lung function, respiratory symptoms, and the menopausal transition," can be found in the articles in press section of the JACI Web site, www.jacionline.org. The JACI is the peer-reviewed journal of the American Academy of Allergy, Asthma & Immunology (AAAAI).

Francisco Gómez Real, MD, and colleagues studied a group of women aged 45-56 years who were not taking sex hormones. The women provided information about their lung health and menstrual history and the ratio of height to weight, body mass index (BMI).

The researchers found:

- Women who had stopped menstruating had significantly lower lung function and more respiratory symptoms than women of the same age who were menstruating regularly.
- Lean women (BMIs of less than 23 kg/m^2) showed a greater risk for lung problems.

The authors speculate that lower lung function in menopausal women could be explained by increased insulin resistance in menopause. Furthermore, because insulin resistance is a proinflammatory condition, this could also explain the increase in respiratory symptoms associated with menopause.

Clinicians should be aware of increased asthma risk and lower lung function in women, especially lean women, reaching menopause.