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Use of adrenaline in allergy

AAITO Committee for "Use of Adrenaline in Allergy Guidelines"

Index

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 likely 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 *likely 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 *known 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

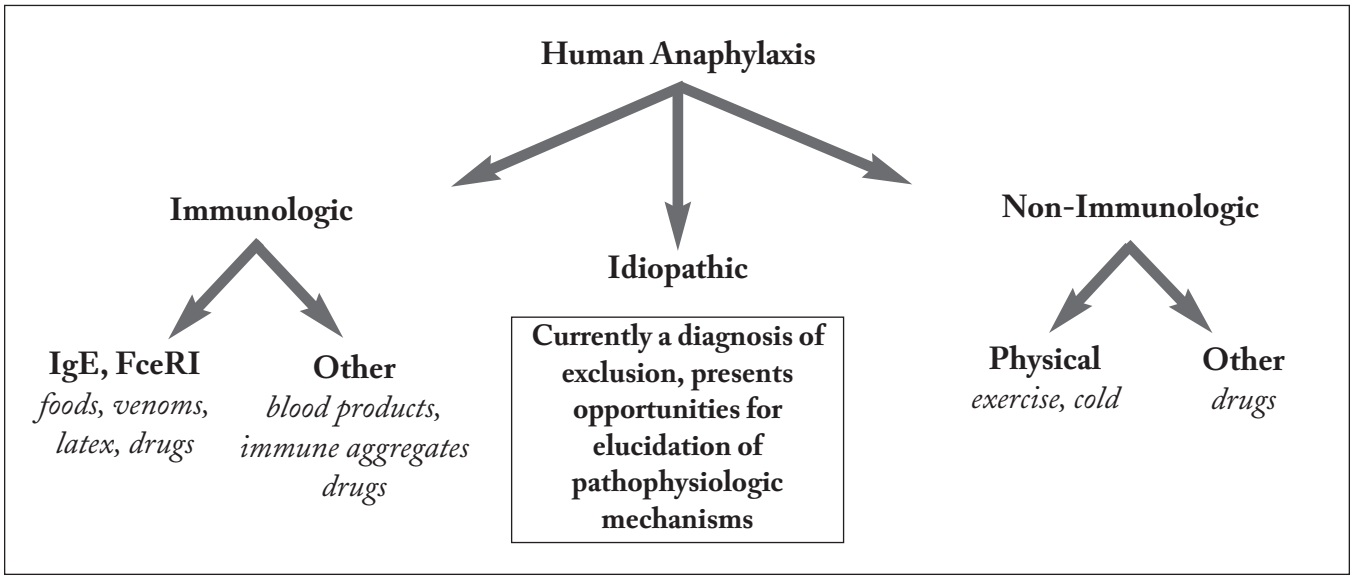
Note that the phrase 'GCS of 11' is essentially meaningless, and it is important to break the figure down into its components, such as E3V3M5 = GCS 11. A Coma Score of 13 or higher correlates with a mild brain injury, 9 to 12 is a moderate injury and 8 or less a severe brain injury.

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 Epidemiology 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 anaphylaxis:

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

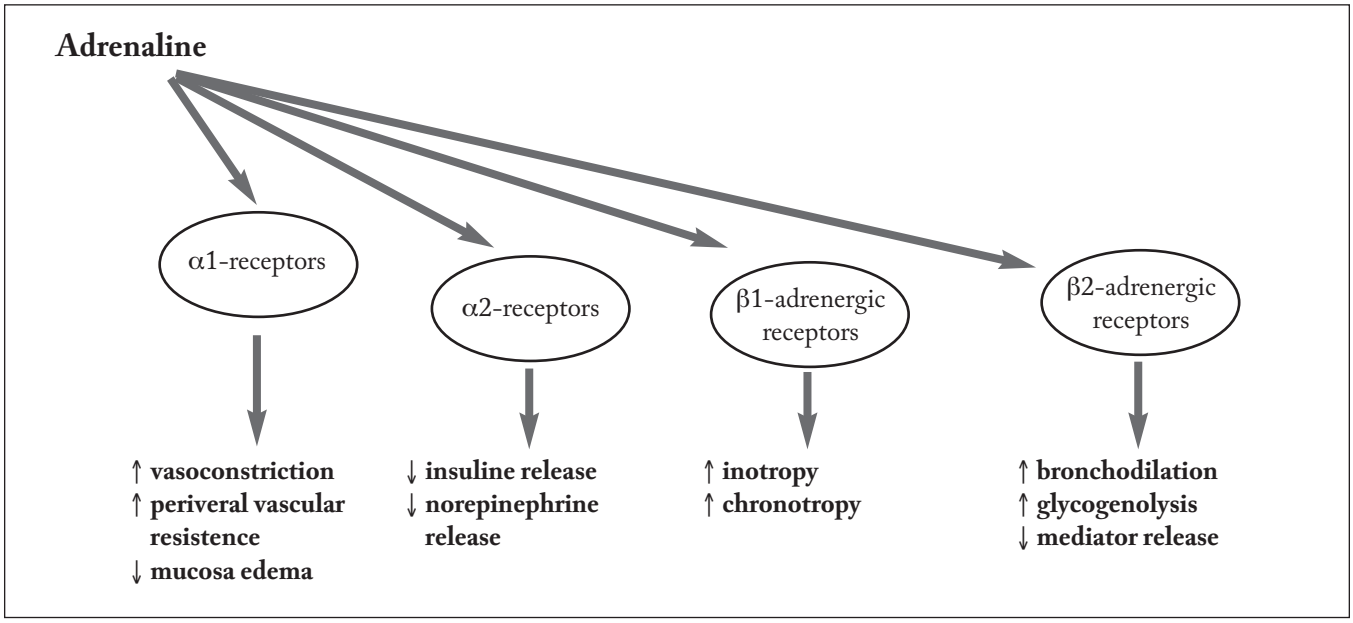
Adrenaline has been considered effective in the treatment of the anaphylactic shock since 1925 (49).
Adrenaline is a direct-acting sympathomimetic α-adrenergic and β-adrenergic agonist with cyclic adenophosphate-mediated complex, bidirectional pharmacologic effects on many target organs. Achieving high 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 adrenaline efficacy by blocking effects at adrenergic receptors.
† Potential interference with endogenous compensatory responses.
‡ Potential increase in adverse effects of adrenaline because of prevention of adrenaline uptake at adrenergic receptors.
§ Side effects are similar to those of adrenaline; amphetamines and methylphenidate release intracellular stores of adrenaline and also block monoamine oxidase, preventing adrenaline 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 concentrations 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 adrenaline 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 adrenaline in individuals actually experiencing anaphylaxis are unethical because prompt treatment with adrenaline 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 adrenaline 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 adrenaline 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 patients 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 adrenaline plasma concentrations similar to those obtained after adrenaline 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 adrenaline 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 labor 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 labor or an abortion
- The use of parenteral (intravenous) adrenaline 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 adrenaline 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. Adrenaline 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 adrenaline for the first-aid, out-of-hospital treatment of anaphylaxis.

Some adolescents and adults may not be optimally treated with the maximum adrenaline 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 adrenaline 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 adrenaline 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 adrenaline 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 adrenaline (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 adrenaline 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 adrenaline should only be prescribed for severe systemic reactions; at the moment there is no consensus about the prescription of adrenaline 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 adrenaline 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 adrenaline 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 adrenaline 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 paragraph 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 gloves 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).

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