

# MANAGEMENT OF ANAPHYLAXIS IN EMERGENCY MEDICINE.\*

*French Society of Emergency Medicine (SFMU) guidelines with the contribution of French Allergology Society (SFA) and the French Speaking Group in Pediatric Intensive Care and Emergency (GFRUP)*

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**Key words:** allergy, anaphylaxis, emergency medicine, epinephrine, guidelines

## ABSTRACT

These formalized expert guidelines were written by the French Society of Emergency Medicine (SFMU), in partnership with the French Allergology Society (SFA) and the French Speaking Group in Pediatric Intensive Care and Emergency (GFRUP). Their goal is to educate emergency physicians to early diagnosis of this potentially fatal reaction of severe hypersensitivity, the specific features associated with age, and risk factors identification. Anaphylaxis diagnosis is clinical and used Sampson's clinical criteria. The authors offer helps sheets for emergency medical services dispatch and triage criteria for emergency department nurses. As underlined by the international guidelines, the main treatment is early administration of intramuscular epinephrine. If an epinephrine auto-injector is available, the emergency medical services dispatch center on-call physician (112-call) should encourage its immediate use. The second line of treatment is based on the eviction of the triggering factor, the appropriate waiting position, oxygen therapy, and depending on the symptoms, fluid therapy, bronchodilator and epinephrine nebulization. The severity of the prognosis and the unpredictability of developments justify the deployment of a mobile intensive care unit. A minimum six-hour hospital observation is indicated. Tryptase kinetics evaluation contributes to a posteriori diagnosis. At emergency department discharge, the patient must have a prescription of an emergency kit (containing two epinephrine auto-injectors and  $\beta_2$ -agonists), written instructions and a detailed written hospital report. A specialized consultation with an allergologist is essential after the emergency department discharge.

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## 1. INTRODUCTION

**Anaphylaxis is a systemic, severe and potentially life-threatening hypersensitivity reaction [1].** It occurs within few minutes to few hours after exposure to an allergen [2]. It is characterized by the sudden onset of airway, and/or circulatory problems. It is usually, but not always, associated with skin and mucosal changes [3]. Gastrointestinal symptoms may also be present [2]. Nevertheless some of these symptoms may vary in severity and may resolve spontaneously. The identification of the trigger factor is sometimes challenging and can remain unknown. For all these reasons under-diagnosis of anaphylaxis is likely to be common resulting in insufficient use of adrenaline (less than one third of anaphylactic cases) [2;4;5]. Finally, before discharge from emergency department (ED), a prescription of an adrenaline auto-injector and referral to an allergy specialist are recommended but not enough performed.

These findings highlight the need to improve health professionals' skills in the diagnosis and management of anaphylaxis [6]. European Academy of Allergy and Clinical Immunology (EAACI) taskforce on anaphylaxis provided evidence-based guidelines for the diagnosis and the management of anaphylaxis [1;3;7]. Our aim was to provide guidelines for the management of anaphylaxis in emergency departments. These guidelines are based on EAACI anaphylaxis guidelines.

### 1.1. Methodology

The French Society of Emergency Medicine (SFMU) is the promoter of these recommendations drafted by the SFMU "*commission des référentiels*". The working group was composed of members of the SFMU Board of Directors and an independent expert panel from French scientific societies: French Society of Allergology (SFA), Francophone Group of Resuscitation and Paediatric Emergencies (GFRUP), French Pediatric Pulmonology and Allergology Society (SP<sup>2</sup>A).

The literature review was conducted using the European and international recommendations as well as PubMed® database. Reviewers were health professionals working in fields related to these recommendations. Proofreading/verification committees validated these recommendations.

### 1.2. Epidemiology

The epidemiological data regarding anaphylaxis are discordant because issued from studies with heterogeneous methodologies (using various populations and diagnostic criteria)

**Prevalence:** In Europe, the prevalence is estimated at 0.3% [3].

**Incidence:** Anaphylaxis incidence is increasing and is estimated to be between 1.5 and 7.9 per 100.000 people per year [3]. Hospitalizations are more frequent in adults than in children: 2.3 per 1000 admissions in adult in the ED vs 1 per 1000 admissions in pediatric ED [8]. Turner et al. analyzed data from a registry

recording all hospitalization admissions and fatalities caused by anaphylaxis in the United-Kingdom between 1992 and 2012. **The number of anaphylaxis-related hospitalization admissions increased 7-fold during this period.** This increase may be partly related to anaphylaxis coding changes (transition from International Classification of Diseases (ICD) ICD9 to ICD10) and the recommendation of minimum 4-hour observation period in ED after an anaphylaxis in United-Kingdom [9].

**Mortality:** In this study, mortality was estimated at 0.047 cases per 100,000 persons per year and the main cause was medications [9]. The median time to onset of cardiac arrest (CA) is 30, 15 and 5 minutes for anaphylaxis fatalities induced by food, insect sting and intravenous (IV) medications, respectively [10]. **Deaths are most often secondary to respiratory distress (86%) in case of food anaphylaxis and to cardiovascular damage in case of anaphylaxis related to medications or insect sting [10].** The first peak of anaphylaxis mortality was noticed between the age of 10 and 30 years due to food and a second peak was noticed after 60 years of age due to medications or insect sting-related anaphylaxis [9]. Nearly the third of food anaphylaxis fatalities occurs in the patient's own home whereas 20% occurs in restaurants [9;11].

**Recurrence:** In the United-Kingdom registry of anaphylaxis fatalities, 69% of fatal cases were known to be food allergic before the fatal event and 20% have experienced a prior anaphylaxis [9]. A North American study conducted in 2014 in patients with a history of anaphylaxis showed that the majority had experienced at least 2 previous episodes of anaphylaxis and 19% of them more than 5 previous episodes [12]. Half of these patients had never had a prescription of an adrenaline auto-injector [12]. The recurrence of anaphylaxis is more common in patients with a food allergy [5].

### 1.3. Triggering factors

**In children, food is the main trigger while medications and insect venom are more common in adults [3].** However the trigger is not identified in 20% of anaphylaxis cases. It varies according to age, and geographical areas [1]. In Europe, the main causes of anaphylaxis are: food (65% in children and 20% in adults), insect venom (20% in children and 48% in adults) and medications (5% in children and 22% in adults) [5]. Antibiotics, especially beta-lactam antibiotics and non steroidal anti-inflammatory drugs are the most commonly involved [3;5]. Nearly all food can trigger anaphylactic reactions by ingestion, inhalation or skin contact with the allergen [13]. Peanut, nuts and milk proteins (cow, sheep and goat) for children under 16 year of age are the most frequently incriminated in severe or even fatal food anaphylaxis [9;14;15]. Some patients may even react to the presence of food allergen traces (peanut in particularly). Latex may also be implicated, particularly in hospital setting.

#### 1.4. Physiopathology

The pathophysiological mechanisms of anaphylaxis are complex and not yet fully understood. Immunologic mechanisms can be distinguished (IgE or non-IgE mediated) from non-immunological mechanisms (direct activation of mast cells) [2]. The main effector cell is the mast cell, but other cells may be involved such as basophils and neutrophils. **However the therapeutic management at diagnosis is not influenced by the suspected pathophysiological mechanisms.**

Classically, anaphylaxis is an allergic IgE-mediated hypersensitivity reaction. During the first contact with the antigen (allergen), clinically silent phase (sensitization phase), IgE are synthesized by B cells and bind to the tissue mast cells and basophils by their high affinity membrane receptor. After a delay, during a second contact, the bridging of IgE by the allergen causes mast cell activation and degranulation, releasing the mediators of the acute phase. Degranulation of the preformed mediators, stored in mast cell granules (histamine, serotonin, chemokines, tryptase, chymase, etc.) is followed by the production of neofomed mediators within minutes (leukotrienes, prostaglandins, thromboxane, platelet activating factor) or hours (cytokines, growth factors) following mast cell activation [16;17]. IgE can recognize an antigen sequence (epitope) common to different allergens, explaining allergic reactions without apparent prior contact. They are called cross-allergic reactions. The detection of IgE in the blood reflects previous contact with an allergen but does not preclude a clinical

**Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:**

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue uvula)

**AND AT LEAST ONE OF THE FOLLOWING**

- a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
- a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lipstongue-uvula)
  - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
  - d. Persistent gastrointestinal symptoms (eg, crampy 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.

\*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Modified from Sampson, et al. [6] Used with permission.

**Table 1:** NIAID/FAAN clinical criteria for the diagnosis of anaphylaxis. [28]

response during subsequent contacts with allergen [18]. The clinical manifestations result from biological actions initiated by the many pro-inflammatory mediators released [19;20]. Histamine is the best known mediator. It plays a major role in the symptomatology. Other mediators potentiate and prolong the action of histamine, with sometimes more powerful effects. The platelet activating factor alone can induce anaphylaxis [21].

These mediators cause contraction of smooth muscles of the digestive tract, bronchoconstriction, airway edema and mucus hypersecretion, vasodilation associated with an increase in capillary permeability responsible for plasma extravasation [19]. The myocardium may be a target member [22], impacted directly or indirectly. The abundance of mast cells could explain early severe cardiac events [23]. Acute coronary syndromes have been described [24].

The mediators involved, the affected organs and the compensatory physiological response of the body (involving the renin-angiotensin-aldosterone system and increased secretion of endogenous catecholamines) determine the symptoms and the severity of anaphylaxis. Pre-existing conditions (asthma, heart disease), extrinsic factors (exercise, infection, alcohol consumption, endocrinologic factors, etc.), ongoing medical treatments and genetic polymorphism may also influence the severity [25;26].

#### 1.5. Clinical diagnosis

Anaphylaxis is a clinical diagnosis. It is characterized by the rapid onset of symptoms and signs affecting multiple organs. It appears within minutes to few hours after exposure to a trigger. This delay varies depending on the trigger itself, its way of entry into the body and on co-existing factors [3]. Isolated mucosal and/or cutaneous changes do not fulfill the diagnostic of anaphylaxis. However, these manifestations should not be overlooked because they may be the first symptoms of anaphylaxis.

Clinical criteria defined by Sampson et al. (**Table 1**) [27] demonstrate an excellent sensitivity (97%) and specificity (82%) for the diagnosis of anaphylaxis in a retrospective ED study [28].

**Annex 1** contains a table of common clinical symptoms that can occur in an anaphylactic reaction. The symptoms may vary from one patient to another and, in the same patient, from one anaphylactic episode to another [2]. There is no reliable predictor for the severity at onset of an allergic reaction and death may occur within minutes irrespective of the initial symptoms [2]. However, the earlier the clinical manifestations appear after contact with the triggering factor, greater is the severity [29].

In this table, most of clinical manifestations involve at least two organs, but sometimes the clinical presentation is limited to a single organ failure [2]. Cardiac arrest, shock with multiple organ failure, respiratory distress (acute asthma or laryngeal dyspnea) or moderate systemic clinical signs particularly digestive [30] can be the main and initial manifestations of

anaphylaxis[8]. Hypotension is a late sign of shock in children so that attention should be paid on other perfusion parameters (heart rate and capillary refill time) [31]. The mucosal and cutaneous manifestations are the most frequently observed changes during an anaphylaxis. However, anaphylaxis can develop in the absence of skin features (15% of anaphylaxis cases) which is frequently associated with delay in the diagnosis and the appropriate treatment with adrenaline [8].

Anaphylaxis may gradually get worse (protracted reaction) within the first hours after initial symptoms or signs or may involve biphasic reactions [2;32]. Biphasic reactions have been reported to develop from 0.4 to 23% of reactions [7]. They usually occur 4 to 12 hours of the first symptoms and signs, up to 72 hours maximum, and can be more severe than initial manifestations. A delay or a failure to inject adrenaline, an insufficient adrenaline dose and/or failure to administer corticosteroids may increase the risk of those reactions [3]. The risk of biphasic reaction justifies a closely monitoring for at least 6hours in the ED after an anaphylaxis [33]. Anaphylaxis may resolve spontaneously.

### Atypical cases

Exercise-induced anaphylaxis is defined as the onset of allergic symptoms during or immediately after exercise. The pathophysiology is poorly understood and the evolution is unpredictable [3]. The reproduction of the same exercise by the same patient does not systematically generate the same symptoms. In some cases, symptoms appear only when the exercise is associated with a second cofactor such as specific food intake (or not), or a nonsteroidal anti-inflammatory drug or pollen exposure [29]. Food-dependent exercise-induced anaphylaxis is a syndrome characterized by a chronological sequence in which food intake, followed by exercise (within four hours) induces symptoms after a varying period [34]. When the food intake and the exercise are independent of each other, there are no symptoms.

Mammalian meat induced ( $\alpha$ -Gal) anaphylaxis is often difficult to diagnose because the allergic reactions manifest as classic immediate-type allergies but with an unusual latency of 3-6 hours following ingestion of meat [35]. The phenomenon of a delayed-onset immediate-type allergy with a latency of 3-6 hours following ingestion of meat is considered pathognomonic for  $\alpha$ -Gal syndrome.

Mast cell disorders are risk factors of anaphylaxis, in particular related to insect venom or medications; anaphylaxis is sometimes challenging in these patients because severe cardiovascular symptoms or signs may occur without any skin changes. In these cases, a baseline serum tryptase should be performed [36]. The differential diagnosis between anaphylaxis with and a vasovagal syncope is sometimes challenging.

Diagnosis of anaphylaxis is often more difficult in infants, with a high frequency of digestive or nonspecific respiratory and skin signs. The clinical spectrum of signs and symptoms may vary from lethargy to sudden death [37].

### 1.6. Differential diagnosis

The clinical manifestations of anaphylaxis are various involving multiple organs so that many differential diagnoses can be discussed [2], including:

- Asthma exacerbation can be confused with anaphylaxis with its usual signs and symptoms (wheezing, cough and dyspnea); however, pruritus, urticaria, angioedema, severe abdominal pain and hypotension are not usually present in asthma exacerbation.
- A panic attack may include a feeling of imminent death, dyspnea, flushing, tachycardia or gastrointestinal symptoms, but it is not associated with urticaria, angioedema, wheezing or hypotension.
- Envenimations, histamine poisoning, scombroid food poisoning (tuna, mackerel), food poisoning, poisoning and shocks from other etiologies [3].
- Non histaminergic bradykinin-mediated angioedema is an entity with different subtypes characterized by localized white non-pruritic swelling, disappearing within 2 to 4 days, which can involve skin or mucosal tissues and usually evolving by crises. The different causes can be inherited or acquired, particularly iatrogenic. Bradykinin-mediated angioedema differs from allergic origin by its clinical features and is unresponsive to conventional treatment with antihistamines, corticosteroids or adrenaline. The diagnosis should not be delayed because health condition may worsen rapidly in case of laryngeal attack, requiring a specific emergency treatment [38].

### 1.7. Classification of severity

Different classifications exist including the historical classification according to the Ring and Messmer 4-step grading scale [39]. They are of no use at the onset of an anaphylaxis and are not included in international guidelines.

### 1.8. Risk factors, aggravating factors

Some comorbidities increase the risk of severe or fatal anaphylaxis: asthma (especially for food allergy in children), cardiovascular disease and mast cell disorders. Some treatments also increase this risk: angiotensin converting enzyme inhibitors and  $\beta$ -blockers [3]. All antihypertensive treatments may increase its severity [40]. Altered metabolism of the mediators of anaphylaxis (tryptase, histamine, platelet activating factor and bradykinin) may explain the severity observed in some cases of anaphylaxis. Cofactors are associated with more severe allergic reactions: exercise, alcohol, nonsteroidal anti-inflammatory drugs, stress, acute infection, fever and premenstrual period [7]. They are observed in up to 20-30% of anaphylaxis cases [1].

## 2. THE MANAGEMENT

The management of IgE mediated anaphylaxis is more specifically described. Nevertheless these recommendations are applicable regardless of the physiopathology mechanism.

### 2.1. Structures of emergency medicine

#### 2.1.1. Service of urgent medical aid (Centre 15): medical regulation of the calls

There are few studies on the treatment of calls suggestive of anaphylaxis. To date, the frequency of calls for severe allergic reaction is unknown in France. The only published data are reported in a study from North America where calls to 911 (phone emergency calls center) for allergic reactions account for 0.4 to 0.9% of annual calls [41].

In order to sensitize stakeholders in emergency medical aid and optimize the processing of these calls, we wished to propose to all Centers of regulation of emergency medical Services (EMS) (Centre 15) calls a form of regulation on the action to be taken with a call concerning anaphylaxis. This form has been made on the model of the sheets of the medical regulatory guide [42]: **annex 2** for assistants of medical regulation, **annex 3** for regulators physicians. As the diagnosis is clinical, announcement of respiratory, cardiovascular, muco-cutaneous or digestive signs or symptoms within few minutes to few hours after exposure to an allergen known or likely, must allow (even in the absence of muco-cutaneous signs combined) to bring it up during the telephone interview.

The rapid onset of signs/symptoms or onset of respiratory/hemodynamic dysfunctions makes it necessary to address this call on a priority basis. In front of symptoms suggestive of anaphylaxis, priority must be given to support the distress. **Emphasis should be placed on the need for an urgent intramuscular (IM) administration of adrenaline [29;43]. There is no absolute contraindication to the use of epinephrine in case of anaphylaxis.** Unlike IM route, the intravenous administration of adrenaline requires titration and cannot be recommended without a trained medical team equipped with electrocardiographic monitoring and a defibrillator.

During the interview with the caller, **the presence of an adrenaline auto-injector (AAI) must be systematically sought.** The caller or the entourage must then be motivated to carry out without delay an IM injection of adrenaline in (re)explaining the use of the AAI (**annex 4**). When a severe allergic reaction occurs at school a personalized care project (PCP) including an emergency kit with AAI should be looked for. **Considering the situation of an anaphylaxis without PCP for the child, the use of an available AIA must be privileged by telephone prescription through the control center 15 (the SAMU).** Some patients at high risk of anaphylaxis have the indication to use the adrenaline by their allergist at the onset of muco-cutaneous or digestive signs (without cardiopulmonary compromise). In all

cases, it is for the regulator doctor to apply this protocol even if there is no major distress at the time of the telephone contact.

**When anaphylaxis criteria are present, we offer a pre-hospital healthcare means in case of respiratory or cardiovascular compromise, or when the symptoms are rapidly evolving.** Important digestive symptoms may be the first clinical signs of shock. In the event of unavailability of a pre-hospital medical means, IM injection of adrenaline should be favored as soon as possible. In the absence of cardiopulmonary disease or rapid evolution of symptoms, rescue workers means will be engaged and the patient will be directed to emergency room (ER) to continue monitoring, perform diagnostic tests and be in a place for secondary preventive measures. When patients present and complain only about mucocutaneous symptoms without anaphylaxis criteria, a telephone advice or a referral to a general practitioner (GP) is possible. The GP must advise the caller to get back to the center 15 of SAMU in case of subsequent worsening because these isolated mucocutaneous signs may be the initial phase of a beginning anaphylaxis.

**In case of diagnostic uncertainty or when the patient is discharged home, a call for monitoring should be performed by the medical control team to evaluate the progression of symptoms.**

#### 2.1.2. Structure Emergency: sorting by the organizer nurse upon admission or when receiving the patient.

The organizer nurse of the reception must know how to identify and search for elements that evoke a probable allergy. **It is necessary to take into consideration the evolving nature of anaphylaxis and treat the patient without waiting for the appearance of vital distress.**

A patient with respiratory, cardiovascular, muco-cutaneous or digestive signs few minutes to several hours after exposure to a known or probable allergen must be put in the room of life-threatening emergencies. The rapidly progressive nature of the symptoms must be sought. In case of isolated but progressive worsening muco-cutaneous signs, the nurse should inform the referring physician. If isolated muco-cutaneous signs, not progressive, the patient can be put in an isolated room. In this case, the receptionist coordinator nurse (RCN) has to inform the patient to report any changes in symptoms.

### 2.2. Treatment

Adrenaline must be administered to all patients experiencing anaphylaxis. It is the first line treatment for anaphylaxis (**Figure 1**). Adrenaline should be given by intramuscular injection into the mid-outer thigh. Other interventions are needed as second-line or third-line interventions include removal of the likely trigger, posture, call for help and other medications [1;43].

There is no absolute contraindication for treatment with adrenaline in case of anaphylaxis. Benefits outweigh the risks even

in the elderly, with cardiovascular disease or pregnant women [2;3]. In the ED, adrenaline is still underused (approximately only 20% of the anaphylactic cases [5]), unlike corticosteroids and antihistamines that are commonly used although they are only recommended as third-line treatment [1;43].

### 2.2.1. Adrenaline

It is the first-line treatment of anaphylaxis [1]. The use of adrenaline derives logically from pharmacological effects described in observational studies, retrospective epidemiological studies, studies using in vitro or animal models, as well as pharmacological studies but out of context of anaphylaxis [2]. There is no randomized placebo study demonstrating the efficacy of adrenaline in the context of anaphylaxis. Patients with anaphylaxis require immediate IM adrenaline [1;7].

Adrenaline exerts effects on the cascade of mediators of anaphylaxis and avoids secondary worsening [1]. An effective clinical response is obtained for the majority of patients after one or two IM injections [2]. Adrenaline should not be used for patients with mild symptoms, for example with only cutaneous or mucosal symptoms without respiratory or cardiovascular compromise. In case of anaphylaxis with digestive symptoms but without cardiopulmonary compromise, the benefit of early use of adrenaline has to be assessed by the physician taking into account the risks for on going anaphylaxis [44]. The IV route has restricted indications. Anaphylaxis fatalities are reported despite prompt treatment with adrenaline [45].

#### 2.2.1.1. Pharmacological actions

Adrenaline has a sympathomimetic direct action. The  $\alpha$ -adrenergic receptors cause peripheral vasoconstriction reversing mucosal edema and hypotension. The  $\beta_1$ -adrenergic receptors increase heart rate and force cardiac contractions reversing hypotension. The  $\beta_2$ -adrenergic receptors induce bronchodilatation and thereby reverse bronchoconstriction and reduce the release of inflammatory mediators [2].

#### 2.2.1.2. Administration time

Adrenaline should be administered as soon as possible. Several retrospective studies analyzing fatal anaphylaxis demonstrated that a failure or delay in the use of adrenaline is a risk factor for fatal anaphylaxis [7;10;11;46]. Administered late in animal models, adrenaline might be ineffective to correct a refractory anaphylactic shock [47].

#### 2.2.1.3. Intramuscular adrenaline

The recommended route of administration is IM [1;7;48;49]. It is efficient, well tolerated [50;51] and easily accessible to all ages especially in infants and children. The use of an AAI is recommended for the treatment of anaphylaxis each time the

device is available. It may save time and secure the delivered dose. The use of AAI is not a medical procedure and injection can be performed by the patient himself or by a non-health professional without any previous training. Adrenaline should be given at the dose of  $10 \mu\text{g}\cdot\text{kg}^{-1}$  to a maximum of 0.5 mg. Considering the marketing authorizations for AAI, the 0.15 mg dose is recommended for patients weighing 15-30 kg and the 0.30 mg dose for those weighing more than 30 kg. Nevertheless, the European Academy of Asthma and Clinical Immunology (EAACI) recommends that patients weighing between 7.5-25 kg should receive a 0.15 mg dose and patients weighing more than 25 kg the 0.30 mg dose [3].

The recommended injection site is the mid-outer thigh [1], even inpatients treated with antithrombotic agents. After adrenaline injection, patients may experience pallor, headache, palpitations, nausea. These transient signs should not be confused with persistent anaphylactic signs [3]. The same adrenaline dose can be repeated after at least a 5-minute interval in case of insufficient clinical response or worsening.

#### 2.2.1.4. Direct intravenous Adrenaline

The IV route is not recommended as a first line treatment and must be given by physicians experienced in the use of vasopressors and require continuous monitoring of oxygen saturation ( $\text{SpO}_2$ ), heart rate and non-invasive blood pressure (NIBP). Immediate access to a defibrillator is also required if needed [29;48]. Adrenaline titration is crucial, because it has a narrow therapeutic window and a various individual susceptibility [48;52]. Intravenous adrenaline may cause serious side effects as follows: ventricular tachycardia or fibrillation, life-threatening hypertension, stroke, pulmonary edema and acute coronary syndrome. The dosage of adrenaline given intravenously in the context of anaphylaxis differs from that required for a CA. Due to the risk of lethal arrhythmia, the IV route must be given exclusively in case of an imminent CA [51], refractory forms or severe hemodynamic instability.

#### 2.2.1.5. Continuous intravenous Adrenaline

The continuous IV adrenaline infusion using automatic needle (IVAN) seems to ensure a sustained improvement of blood pressure while IV pulses of adrenaline have an immediate but short effect on blood pressure with a higher risk for arrhythmias [53]. Perfusion through IVAN must quickly be replaced by IM adrenaline if repeated injections do not improve hemodynamic parameters [2;44;53]. Adrenaline dosage using IVAN must be adjusted to the clinical response. In case of shock, the mean arterial pressure target is at least 60-65 mmHg in adults [52].

#### 2.2.1.6. Aerosol or Nebulizers

Inhaled adrenaline is not recommended for the treatment of anaphylaxis. Nevertheless nebulized adrenaline can be used in patients experiencing a laryngeal edema in addition to IM adrenaline [3;44].

### 2.2.1.7. Synthesis

	Dosage	Practical arrangements	Time elapse for the second dose according to clinical response
Intramuscular	AIA 7.5 to 25 kg: 150 $\mu\text{g}$ AIA > 25 kg: 300 $\mu\text{g}$		5 to 10 minutes
	0.01 $\text{mg.kg}^{-1}$ maximum 0.5 mg	Undiluted syringe 1 mL = 1 mg	
Direct Intravenous	Bolus of 1 $\mu\text{g.kg}^{-1}$	0.1 mg diluted in 10 mL = 10 $\mu\text{g.mL}^{-1}$	1-2 minutes
IV in the automatic needle (IVAN)	0.1 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$		Adapt the flow rate
Nebulization	Minimum 0,1 $\text{mg.kg}^{-1}$ maximum 5 mg	No marketing authorization	20 minutes

**Table 2:** Adrenaline for anaphylaxis in children

AAI = adrenaline auto-injector in France: Anapen®, EpiPen®, Jext®

	Dosage	Practical arrangements	Time elapse for the second dose according to clinical response
Intramuscular	AIA > 25 kg: 300 $\mu\text{g}$		5 to 10 minutes
	0.01 $\text{mg.kg}^{-1}$ maximum 0.5 mg	Undiluted needle 1 mL = 1 mg	
Direct Intravenous	Bolus of 50 $\mu\text{g}$	1 mg diluted in 20 mL = 50 $\mu\text{g.mL}^{-1}$	1-2 minutes
IV in the automatic needle (IVAN)	0.05 to 0.1 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$		Adapt the flow rate
Nebulization	2-5 mg	No marketing authorization	20 minutes

**Table 3:** Adrenaline for anaphylaxis in adults

AAI = adrenaline auto-injector in France: Anapen®, EpiPen®, Jext®

## 2.2.2. Complementary therapies

### 2.2.2.1. Removal of the trigger

Stop current perfusion (antibiotic, radio-opaque contrast or gelatin for example) or eliminate all contact with latex is imperative. Patient should not be encouraged to vomit in case of allergen ingestion [13]. Removing stinger in case of a insect sting is debated because of a potential risk of worsening.

### 2.2.2.2. Securing the upper airways and oxygen therapy

Securing the upper airways is a crucial task, mainly in children that are at higher risk of airway obstruction. High-flow oxygen

should be administered by face mask to all patients with anaphylaxis [1]. In anaphylaxis with upper airways involvement, intubation can be challenging due to a laryngeal edema and requiring sometimes subglottic procedures.

### 2.2.2.3. Volume expansion

In case of cardiovascular instability after the first IM adrenaline injection, intravenous fluids should be administered using either isotonic saline solution or lactate ringer solution at a dose of

20 mL.kg<sup>-1</sup> for adults and children. This volume expansion should be given fast [29] with the first 5 to 10 mL.kg<sup>-1</sup> being infused within the first five minutes. In patients with heart failure, a particular attention should be paid when giving isotonic saline solution. This volume expansion should be repeated if needed to achieve pressure target [3].

#### 2.2.2.4. $\beta$ 2-agonists rapid action or release

Inhaled short-acting  $\beta$ -2 agonists should be additionally given to treat bronchospasm in patients with anaphylaxis [3]. In case of refractory bronchospasm, recommendations on the treatment of an acute severe asthma should be considered [54].

#### 2.2.2.5. Postures

Without delaying the adrenaline injection, the patient should be kept still and positioned according to these features:

- sitting up position if respiratory distress,
- lying on back with the lower extremities elevated (Tredelenburg position), avoiding sudden abrupt change if circulatory instability [55],
- position on the left side with lower extremities elevated if pregnant,
- lateral position if unconscious

### 2.2.3. Other treatments

#### 2.2.3.1. Corticosteroids

Corticosteroids are commonly used for anaphylaxis to prevent protracted or biphasic reactions even if this has not been yet proven [2;3;43]. When given, oral (prednisolone) or IV (methyl prednisolone) corticosteroids are used at the dose of 1 to 2 mg.kg<sup>-1</sup>.

#### 2.2.3.2. Antihistamines

Systemic H1 antihistamines are commonly used but their effectiveness on anaphylaxis has never been demonstrated [3]. They are only effective to relieve cutaneous symptoms. Moreover some cases of hypotension caused by intravenous injection of antihistamines have been reported. This may be related to the speed of injection [3]. Therefore only oral antihistamines are recommended to relieve cutaneous symptoms.

#### 2.2.4. Monitoring

Patients experiencing anaphylaxis should be initially monitored with continuous scope, SpO<sub>2</sub> and NIBP measurements every one to five minutes. A central intravenous line or an intraosseous access should be done in case of anaphylaxis in adults and in the absence of rapid improvement in children. An electrocardiogram

(ECG) should be performed to identify a myocardial anaphylaxis provided that adrenaline is not delayed [24].

### 2.2.5. Particular forms

#### 2.2.5.1. Cardiac arrest

The management of CA should refer to the international updated recommendations [48].

#### 2.2.5.2. Refractory anaphylactic shock

Despite repeated adrenaline injections, continuous adrenaline infusion and a suitable expansion volume, the anaphylactic shock is considered refractory when the mean blood pressure remains below 60 mmHg in adults, and less than the normal in children [2;16;52].

The following measures can be proposed in association with previous ones:

- Norepinephrine at an initial dose of 0.1  $\mu$ g.kg<sup>-1</sup>.min<sup>-1</sup>
- Patients treated with  $\beta$ -blockers may require increased doses of adrenaline due to competitive antagonism receptors  $\beta$ . If anaphylaxis is unresponsive to adrenaline, glucagon may be used for its chronotropic and inotropic effects at a dose of 1 to 2 mg every 5 minutes and then 5 to 15  $\mu$ g.min<sup>-1</sup> IVAN for adults [52]
- Furthermore, some experts suggest in children the dose of 0.03 to 0.1 mg.kg<sup>-1</sup>.min<sup>-1</sup> (up to 1 mg per dose) [56].
- Experimentally, methylene blue may be effective against vasoplegia at a dose 1.5 mg.kg<sup>-1</sup> (direct IV) but this is not recommended in clinical practice [57]

#### 2.2.5.3. Anaphylactic shock in pregnancy

The treatment of the hemodynamic disorders in pregnant woman is identical to that previously described, including adrenaline injection, oxygen therapy and volume expansion [43]; Ephedrine formerly given in this context is not yet recommended by the French Society of Anaesthesia and Intensive Care [52]. Hemodynamic disorders must be rapidly corrected with a closed monitoring for fetal cardiac activity, to define the best measures to be taken obstetrically [58].

#### 2.2.5.4. Kounis syndrome

The anaphylactic inflammatory mediators may induce coronary spasm, rupture of atherosclerotic plaque and coronary occlusion [24]. The ECG performed as soon as possible contributes to the diagnosis of acute coronary syndrome (Kounis syndrome). Therefore, the priority is to treat the anaphylaxis first, and then to discuss the transfer to a technical platform qualified for interventional cardiology.

### 2.2.5.5. Reversible cerebral vasoconstriction syndrome and Tako-Tsubo's syndrome

These syndromes that may occur during anaphylaxis have been reported in the literature. These have been described in anaphylaxis, after adrenaline injection or not, and also in other situations of acute stress [59;60].

### 2.2.5.6. Bezold-Jarisch reflex

This reflex involves a variety of cardiovascular and neurological processes that cause hypopnea and bradycardia. The treatment requires correction of hypovolemia and injection of adrenaline by titration. The administration of atropine in the early stage may lead to CA and is therefore not recommended [16].

### 2.2.5.7. Anaphylaxis in resolution

The diagnosis of atypical anaphylaxis presentation is sometimes challenging leading to an under diagnosis and consequently an under treatment. The administration of adrenaline should be discussed case-by-case [44]. Close clinical monitoring is required and measurement of tryptase may be of aid for the diagnosis of atypical presentations or presentations without clear identified trigger.

### 2.2.5.8. Anaphylaxis in patients with severe ischemic heart disease

With the exception of a vital compromise, the benefit risk of adrenaline for these patients should be evaluated carefully case-by-case [2;61].

### 2.2.6. Algorithm support for anaphylaxis in the ER (Figure 1)

## 2.3. Additional specific tests

Certain mast-cell mediators including tryptase, histamine, and platelet-activating factor have been reported to be elevated in anaphylaxis. The dosage of these biomarkers is not helpful for the diagnosis or the treatment immediately in the emergency service. Moreover it should not delay the treatment with adrenaline. However, it is useful as an argument to achieve the correct diagnosis especially when the clinical presentation is atypical. **A normal level of these markers does not exclude the diagnosis [1].** The sensitivity of these biomarkers varies with the severity of the reaction, the higher sensitivity being obtained for severe reactions. Blood samples collected in the immediate course of the reaction are not renewable and are considered valuable. Their kinetic analysis is essential for the interpretation of the results that requires an organized network. These samples will not be processed urgently by the laboratories and the results will not be available before several days. It is useful to establish a procedure with the laboratories for the collection of samples and transportation.

### 2.3.1. Tryptase

Tryptase is the most important protease stored in the mast cell granules. Its level increases significantly from 15 minutes after the clinical onset with a peak within two hours [62]. The tryptase half-life is approximately two hours. It is of interest to interpret the level of tryptase over time with a basal tryptase level obtained at least 24 hours after the onset of the reaction [63-65]. The tryptase level during the reaction may not exceed the upper reference value, especially in food anaphylaxis [3] or in mild reactions [2]. Normal serum tryptase level can also be obtained if the measurement is performed too early within 30 minutes from the onset of the anaphylactic reaction. Blood samples should be performed in immediate post-mortem for suspected cases of anaphylaxis [66;67]. A mast cell disorder should be suspected in patients with increased basal serum tryptase levels [36].

#### *In practice:*

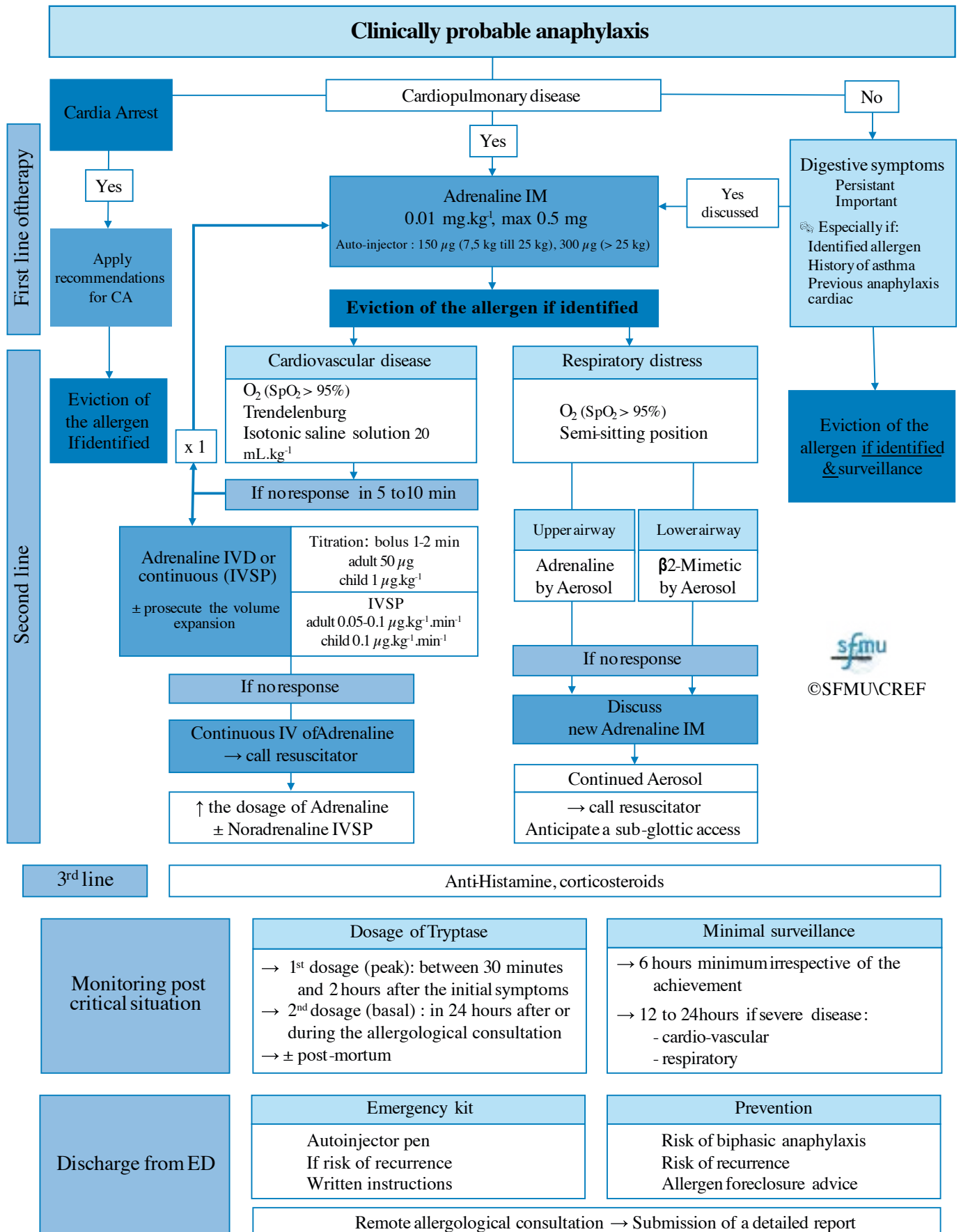
1. Withdraw the blood in a dry tube or EDTA;
2. Stamp the tube with date and time;
3. Fill in the date and time of the onset of symptoms;
4. Send to the laboratory within 48 hours at room temperature.

- **First sample (reaction serum tryptase level):** within 30 minutes to two hours after the onset of clinical symptoms but a sample up to four hours is still acceptable. Do not collect blood samples within the first 30 minutes from the onset of symptoms to avoid false negative results.

- **Second sample (basal serum tryptase level):** 24 hours after resolution of symptoms or during the medical consultation by an allergist.

### 2.3.2. Histamine

The increase in plasma histamine reflects the degranulation of mast cells and basophils. The release is immediate with a very short half-life (15 to 20 minutes). The measurement is not performed in daily practice by all laboratories. The blood samples should be collected using EDTA tube and transported at a 4°C temperature as quickly as possible to the laboratory for freezing. The histamine release is proportional to the severity of anaphylaxis. This measurement is useless in pregnancy (after 20 weeks until delivery) and in patients treated with massive doses of heparin (cardiopulmonary bypass) because of false negatives. There are also false positives in case of hemolysis or bad conditions for the conservation/transportation of the blood samples [67]. Since 2015, this measurement is not reimbursed by the French social security services.



**Figure 1:** Initial management of probable anaphylaxis

## 2.4. Monitoring and hospitalization

### 2.4.1. Monitoring modalities in an emergency structure

Initial monitoring includes continuous monitoring of the heart rate, the respiratory rate, the SpO<sub>2</sub> and the NIBP every one to five minutes [2;13;29]. Particular attention should be given to the onset or recurrence of mucocutaneous or digestive symptoms at regular intervals (every 30 minutes for example). This recommendation is based on an expert agreement (Grade D).

### 2.4.2. Monitoring time

Patients who presented with anaphylaxis should be closely monitored for at least six to eight hours after resolution of their symptoms [3;33;68]. In the case of cardiovascular compromise, a close monitoring for at least 12 to 24 hours is recommended [3]. These recommendations are also based on an expert agreement (Grade D).

### 2.4.3. Instead of monitoring

According to local organizations of emergency services, patients experiencing an anaphylaxis should be monitored in the emergency room, short-term hospitalization units, in pediatric service, in continuous surveillance units or in intensive care unit depending on the initial severity. This recommendation is based on an expert agreement. In case of anaphylaxis with a severe cardiovascular or respiratory compromise, a contact with an intensive care physician should be provided [3].

## 3. DISCHARGE CARE POST-EMERGENCY

At the end of the initial support, information and education time is necessary. The person responsible for this information and the place of education are defined according to local organizations.

- Patients with anaphylaxis should be provided with a discharge advice sheet (**annex 5**) including: 1. Allergen avoidance measures (if any suspected), 2. List of food and medication given, 3. The symptoms of anaphylaxis and instructions for when and how to use an AAI, 4. Information on the potential risk for a biphasic reaction. Patients should be referred to an allergy specialist to investigate the suspected triggers and provide education covering self-treatment of anaphylaxis recurrence and management of concomitant allergic diseases. The AAI should be prescribed for patients experiencing anaphylaxis and its use should be demonstrated (<https://www.YouTube.com/watch?v=iiwgi4UB52w>, accessed 11/05/2016, courtesy of C. Quequet).

### 3.1. Emergency kit

Patients should be informed on the need to carry their emergency kit and especially their AAI always with them [13;29;43]. All

patients experiencing an anaphylaxis should have been prescribed two AAI in their emergency kit. However, this can be discussed in particular in case of anaphylaxis caused by medications when the allergen is well identified and easily avoidable (radiocontrast agent for example).

Inhaled bronchodilators should always be associated in the emergency kit with adrenaline for the majority of allergy specialist, even if the patient had no history of asthma before. There is no medical consensus on the prescription of other drugs commonly prescribed in the emergency kit, as antihistamines and corticosteroids. **The emergency kit for anaphylaxis should always include at least:**

- Written instructions on when and how to inject adrenaline using AAI
- Prescription of AAI with a correct dosage depending on the weight of the patient [3]. French Health Authorities also recommend systematically the prescription of two AAI for each patient experiencing an anaphylaxis [33] (**annex 5**);
- **Inhaled bronchodilators should be associated with adrenaline in the emergency kit, even for non-asthmatic patients.**

### 3.2. Medical prescription before discharge

Medical prescription before discharge includes:

- Two AAI prescribed in accordance with EAACI anaphylaxis guidelines [3]:
  - between 7.5 and 25 kg: 150 µg;
  - over 25 kg: 300 µg;
- Inhaled bronchodilators if bronchospasm.

Oral corticosteroid (prednisolone or prednisone, 1 mg.kg<sup>-1</sup> per day, maximum 60 mg) and oral antihistamines are usually prescribed for three to five days, in order to treat mucocutaneous symptoms and to prevent late clinical reactions. Nevertheless no previous study has evaluated the impact of this treatment after the resolution of the symptoms [44].

### 3.3. Avoidance of allergen

Before discharge, the physician should inform the patient and/or his family about the life threatening risk of an exposure to the same allergen and the importance to avoid any further contact with suspected allergens. **The risk of cross-allergies should also be mentioned.** Referral to an allergy specialist is required to investigate possible triggers and confirm the allergens using validated in vivo and/or in vitro tests interpreted according to a detailed allergy history. The allergy specialist should ensure that the patients are well-trained to prevent any further reactions and, if any, to be able to treat the symptoms adequately. If food is involved, referral to a dietitian should be also advised.

### 3.4. Written report

A written report must be provided to the patient or his legal representative before discharge from the emergency unit. A copy should be sent to the family doctor as well as to the allergy specialist. It should include:

- The diagnosis;
- The triggering factors (if exposed to any medication or food);
- The risk factors and co-factors;
- The clinical symptoms and their severity;
- The results of the biological tests even if pending results (serum tryptase level, etc.);
- The treatment given to the patient (volume and type of fluids, adrenaline, antihistamines, corticosteroids, etc.);
- The length of stay in the emergency unit and monitoring;
- The copy of the discharge prescription.

In children, a brief report should be written in the Child Health Record when available.

### 3.5. Referral to an allergy specialist

The management of anaphylaxis is not limited to the treatment of an acute episode. The referral to an allergy specialist is essential and should be proposed to all patients experiencing an anaphylaxis before discharge from the emergency unit. A care network between emergency physicians and allergy specialists should be ideally organized to follow up such patients [1;30].

The allergy specialist has to investigate the potential triggers and cross-allergies, the immunological mechanisms of the previous reactions, to evaluate the individual risk factors and risk of recurrence, and allergic comorbidities. Patient education about

preventive measures is an important component of the follow up by the allergy specialist. After the evaluation, the allergist can remove the diagnosis of allergy due to a non-convincing history or biological tests not in accordance with the diagnosis. Consumption of some food or use of medications, previously forbidden as suspected triggers after an allergic reaction, can be secondarily authorized by the allergy specialist. A wrong diagnosis of allergy can lead to over exclusion of some food or medications that will have a significant impact on the quality of life of these patients [69;70].

**The severity of an allergic reaction in case of recurrence is unpredictable. Therefore, patients with an allergic reaction without anaphylaxis criteria should be also referred to an allergy specialist before discharge of the emergency service.**

### 3.6. Reporting to the medical aid Service

In order to provide an adequate and prompt treatment from the emergency services, the patients at high-risk of severe anaphylaxis should be ideally recorded as remarkable patients by the SAMU departments. The experts regret the absence of a national registry identifying the patients at high risk of anaphylaxis. This raises legal matters and would have been declared to the French Data Protection Authority (CNIL). This project remains to be addressed.

### 3.7. Allergy Vigilance network

Any side effect or adverse reaction after the use of medications, biological, or cosmetic products should be reported to the national agency of the medicine and healthcare products in France. This declaration can be done online. All anaphylaxis cases, in particular food-induced, can also be reported to the Allergy Vigilance network (Reseau@allergyvigilance.org).

**Annex 1:** Symptoms of anaphylaxis: **The mucocutaneous signs** are frequent (84%) [2;3]. However, anaphylaxis can occur in the absence of cutaneous signs in about 15% in children of also in adults with cardiovascular failure [16;31;52].

Symptoms and frequency	
Subjective signs	<ul style="list-style-type: none"> <li>- Vertigo, anxiety, feeling warm, feeling of imminent death</li> <li>- Metallic taste in the mouth</li> <li>- Palmo-plantar pruritus.</li> </ul>
Muco-cutaneous signs (84% of cases)	<ul style="list-style-type: none"> <li>- Erythema or skin rash</li> <li>- Maculopapular skin rash, urticaria</li> <li>- Generalized hives (angioedema), better seen in areas where the skin is thin (eyelids, ears)</li> <li>- Paresthesia of the oropharynx</li> <li>- Swelling of lips, tongue or uvula</li> <li>- Conjunctival hyperemia.</li> </ul>
Cardiovascular signs (72% of cases)	<ul style="list-style-type: none"> <li>- Tachycardia, bradycardia (Bezold-Jarish reflex), arrhythmia, palpitations</li> <li>- Hypotension, collapse, shock, loss of consciousness</li> <li>- Chest pain, ECG abnormalities (repolarization, conduction)</li> <li>- Cardiac arrest.</li> </ul>
Respiratory signs (68% of cases)	<ul style="list-style-type: none"> <li>- Upper airway: rhinorrhea, nasal congestion, cough, sneezing, itching and pharyngeal discomfort, dysphonia, hoarseness, laryngeal dyspnea, stridor</li> <li>- Lower respiratory tract: tachypnea or bradypnea, dyspnea, cough, bronchospasm, stridor, reduced peak expiratory flow, talking difficulties</li> <li>- Cyanosis, respiratory arrest.</li> </ul>
Digestive signs (45% of cases)	<ul style="list-style-type: none"> <li>- Abdominal pain, nausea, vomiting, diarrhea, dysphagia</li> <li>- Regurgitation in infants.</li> </ul>
Neurological signs (15% of cases)	<ul style="list-style-type: none"> <li>- Confusion, change in behavior, irritability, headache</li> <li>- Restlessness, Vertigo</li> <li>- Drowsiness, lethargy in infants</li> <li>- Altered vigilance, convulsions.</li> </ul>

**Annex 2:** Anaphylaxis regulation sheet-Medical assistant

**ANAPHYLAXIS PROTOCOL**  
**MEDICAL ASSISTANT**

1. Identify the caller, the patient, the location of the intervention
2. Collect information on:
  - The allergic history
  - The nature, time of onset and worsening clinical signs
  - Exposure to an allergen<sup>1</sup>
3. Determine the priority level of the initial call

<b>P0: Cardio-Respiratory Arrest</b>		
<b>P1</b>	History of Allergy	- Patient exposed to allergen <sup>1</sup> or occurrence of urticaria - Rapid evolution of facial edema - Digestive signs, cardiovascular, respiratory allergic reaction for an infant with the project of individualized AAI is done
	No History Of Allergy	- Rapid progression of symptoms - wheezing, debilitating cough, hoarseness of the voice, difficulty in swallowing/ speaking, hypotension, vertigo, incontinence - Edema, abdominal pain, vomiting, diarrhea, skin rash, hypotonia
	In case of allergic risk, the family panics	
<b>P2</b>	- Isolated skin rash provoked by exposure to an allergen - Facial edema without dyspnea, nor difficulty in swallowing or even modification in the voice - Local edema after bee or wasp bite - Ask for advice about allergic risks	

**Table: Prioritization** of the initial call for anaphylaxis determined by the medical assistant.

<sup>1</sup>The main triggers of anaphylaxis are the following: food, medications, insect venom, latex.

4. Advices waiting for the medical regulation:
  - Reassure, not to leave the patient alone
  - Monitor the progression of the symptoms

Lay person down (with legs up if possible); in case of respiratory symptoms, allow the patient to sit up but not to stand; lateral sided security position in case of reduced consciousness.

Apply the degraded procedures if a medical ambulance is not available and send the nearest rescuers in case of respiratory compromise, neurological signs or facial swelling.

**Annex 3 (1/3):** Anaphylaxis regulation sheet- regulating doctor**REGULATING GUIDELINES FOR ANAPHYLAXIS****Regulating doctor**

Anaphylaxis is a **life-threatening clinical emergency** but sometimes it can be **latent** with unpredictable progression.

Anaphylaxis criteria as defined by Sampson et al. (Table 1) [27] are worldwide accepted. These criteria demonstrate excellent sensitivity (97%) and a good specificity (82%) [28].

**Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:**

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue uvula)

**AND AT LEAST ONE OF THE FOLLOWING**

- a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
- a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lipstongue-uvula)
  - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
  - d. Persistent gastrointestinal symptoms (eg, crampy 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.

\*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Modified from Sampson, et al. [6] Used with permission.

**Table 1:** NIAID/FAAN clinical criteria for the diagnosis of anaphylaxis [29].

R1	Anaphylaxis according to Sampson criteria
R2	Evolution of an allergic reaction without the criteria of anaphylaxis
R3/R4	Non-progressive muco-cutaneous allergic reaction to recent appearance

1. Determine the level of response to the emergency call for anaphylaxis by the medical coordinator :

**Annex 3 (2/3):** Anaphylaxis regulating sheet–regulator doctor

2. Medical advice:

- Educate the patient and guide him about the first aid;
- Check for an adrenaline auto-injector, prescribe it and help the patient and/or his family to inject adrenaline
- Prescribe and help any caregiver to administer adrenaline intramuscularly in care facilities.
- Remove allergen: stop infusion, avoid contact with latex, and do not induce vomiting if swallowed. In case of insect sting, removal of the stinger is debatable.

**The known allergic patient:**

→ **for all anaphylaxis cases, IM adrenaline injection is necessary as soon as possible.**

- Administer adrenaline with an AAI if available; make sure that the family or caregiver knows how to use the device, to avoid failure injection. The AAI can be used by the patient himself or by any other person who is present. It is not a medical procedure;
- In case of bronchospasm, the inhaled bronchodilators ( $\beta_2$ -agonists) must be given quickly in addition to adrenaline injection;
- Antihistamines and corticosteroids are not recommended for the initial treatment of anaphylaxis but are only recommended for the relief of cutaneous symptoms.

## 3. Investigation and level of care expected by the first professional assistance:

- Rescuer assessment of vital signs, adequate and comfortable position and oxygen if needed.
- In case of anaphylaxis and availability of an AAI, encourage its use.

## 4. Investigation and immediate requirement by the emergency medical team:

- Anaphylaxis: administer immediately IM adrenaline if not given before (if no improvement, administer the 2<sup>nd</sup> injection within 5-10 minutes);
- To treat according to clinical signs (cardiovascular or respiratory): volume expansion with normal saline, oxygen therapy, and  $\beta_2$ -agonists;
- Remove the allergen;
- Perform an ECG (myocardial anaphylaxis), without delaying the adrenaline injection;
- Antihistamines and corticosteroids are not first-line treatment of anaphylaxis.

**Annex 3 (3/3):** Anaphylaxis regulating sheet-dispatching center emergency physician**Orientation and follow-up**

## 1. Patient orientation criteria:

- If prolonged hemodynamic or respiratory compromise:  
→ Resuscitation, the patient is transferred to an intensive care unit for monitoring and treatment
- In other cases:  
→ the adult patient will stay in the emergency room, for a medical monitoring for at least six hours.

2. Follow-up: advice to recall the emergency medical assistant service (SAMU, 15) in case of worsening or recurrence of symptoms. If any doubt or when the patient remains at home, a follow-up call should be provided by the medical coordinator in order to assess the progression of the symptoms.

**The reasoning tools**

Anaphylaxis can develop without skin involvement; gastrointestinal signs may also be associated with anaphylaxis. Respiratory (mainly for food-induced anaphylaxis) and cardiovascular (mainly for medication- or insect venom-induced anaphylaxis) signs or symptoms are the potentially life-threatening features of anaphylaxis. Symptoms and signs of food-induced anaphylaxis usually occur within 30 minutes from exposure to the allergen.

To assess cofactors and risk factors for severe allergic reactions, including:

- Extreme ages, adolescents;
- Comorbidities (mastocytosis and mast cell disorders, asthma, cardiovascular diseases);
- Treatment with  $\beta$ -blocker or ACE inhibitor;
- Specific allergens most commonly involved in food-related fatal cases: peanuts, nuts, milk proteins.
- Remote areas and lack of rapid access to medical assistance.



### INSTRUCTIONS BEFORE DISCHARGE FROM THE EMERGENCY AFTER A SEVERE ALLERGIC / ANAPHYLAXIS REACTION

Identity of the patient	<b>Appointment with the allergist:</b> Phone: The appointment date & time: Place:
-------------------------	--

You have been hospitalized for a severe allergic reaction, which may exceptionally recur within 2 to 3 days. Consult an allergist to confirm or not this allergy, to identify the suspected agent and to get a management plan, training and advices. The physician must list the allergen(s) that might be involved in this reaction.

WRITE HERE THE FOODS AND MEDICATIONS THAT YOU HAVE TAKEN IN THE HOURS PRECEDING THE REACTION:

Until you go to the appointment, help the doctor, point out the possible causes of your allergy that you should avoid.

An emergency kit with two adrenaline auto-injectors (EpiPen®, Jext®, Anapen®) is prescribed:

ENTER HERE THE NAME OF THE PEN AND ITS DOSE

They should be hold with you all the time. They are used only when new SEVERE allergic reaction occurs.

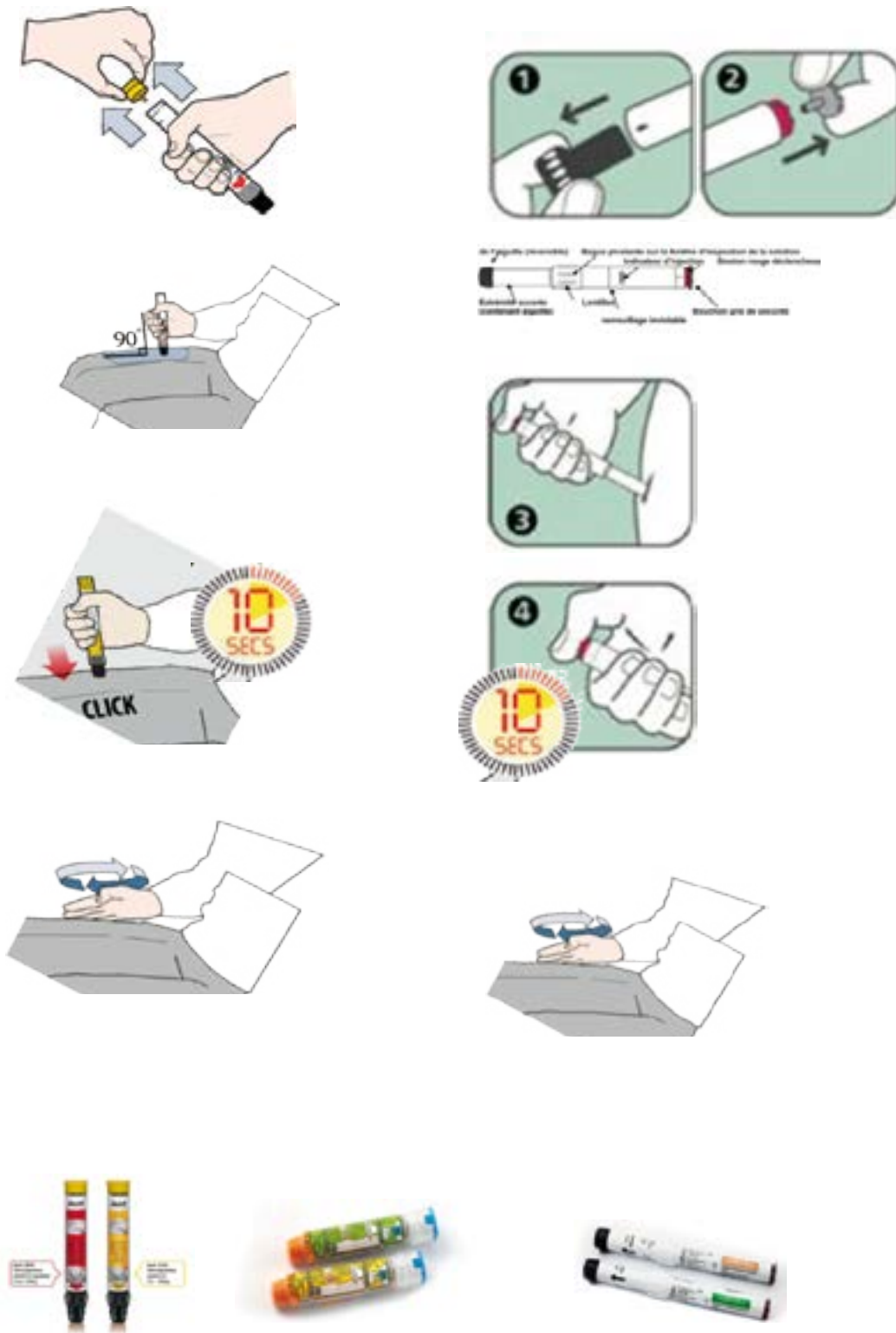
		Signs of allergy, how to react
<b>Allergy Without severity</b>	If acute onset after contact with the suspected agent (allergen): hives, itchy pimples, redness, red eyes, sneezing	
	If appearance of edema, swelling of the face, hands, eyes, etc.	No injection of adrenaline → Take an antihistamine + corticosteroids
<b>Severe allergy</b> <i>Instructions to customize</i>	In case of: difficulty in breathing, asthma, wheezing, and swelling of the throat with a difficulty to swallow, speaks, breathe	→ calm the patient & semi-sitting position
	In case of onset feeling of malaise, dizziness, or sudden weakness	→ Lye the patient & elevate the legs
	Call the ambulance number 15 or 112 - Explain your allergy - Say you have a pen of adrenaline	Do the pen of adrenaline injection: in the middle of the outer side of the thigh, Keep the pen pressure 10 seconds
	If no improvement after 5 to 10 minutes	→ Repeat the injection of adrenaline
	In case of respiratory distress (asthma, etc.)	→ Take:

<b>Other instructions, special case:</b>	Permission to register as a «remarkable patient» with SAMU the place of residence: <input type="checkbox"/> Yes <input type="checkbox"/> No	Signature of the patient:
	Date:  Stamp the name & signature of the emergency room physician:	

Annex 5 (verso): A copy to keep in the medical record

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THE ADRENALINE AUTO-INJECTORS



Date:

Stamp, the name and the signature of the emergency room physician:

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