

Anaphylaxis and Anaphylactoid Reactions

Classification and Pathophysiology

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Introduction

The first documented allergic individual in history might have been Pharaoh Menes, 2640 BC, who, as hieroglyphes tell, died from the sting of a wasp (1,2). Other cases of lethal hypersensitivity reactions have been described in the history of medicine for several thousand years (3). However, it was only in 1902 that Richet and Portier conducted their experiments on the yacht of Prince Albert of Monaco in order to find protective immunization against the poison of the tentacles of actinaria (4,5). Instead of a protective influence, the dogs died a few minutes after the second administration of a small dose of the extract. Richet named this dramatic phenomenon "anaphylaxis" in order to distinguish it from the opposite, i.e., protection (= "phylaxis") and received the Nobel prize for these studies (5).

In 1910 Dale and Laidlaw reported that the *in vivo* effect of a new substance named histamine clearly resembled the symptoms of anaphylaxis (6). In 1921 Prausnitz and Küstner discovered that this immediate-type hypersensitivity was transferable by a serum (1,3). More than 40 yr later this reaginic activity was identified as immunoglobulin E by Ishizakas and Johansson (1). However, it was soon clear that apart from immunologically mediated hypersensitivity, clinically similar reactions could be elicited, which then were called pseudo-allergic reactions by P. Kallos (7).

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Definitions

Anaphylaxis represents the maximal variant of a systemic immediate-type allergic reaction.

In the literature, the term "anaphylaxis" has been used variably (8,9):

1. To describe the clinical syndrome of acute systemic reactions following allergen exposure, and
2. To define an immunologic pathomechanism; more specifically, to define an IgE-mediated immediate-type reaction.

In most of the classical IgE-mediated anaphylactic reactions these two conditions are fulfilled. However, in pseudoallergic hypersensitivity reactions, the clinical symptoms, but not the immunological mechanism, resemble anaphylaxis (7,10). Therefore, we prefer the term "anaphylactoid" as a clinical description of symptoms resembling the symptoms of anaphylaxis, irrespective of the pathomechanism involved. It should be stressed that some authors use these definitions differently (11–13).

Pseudoallergic reactions are hypersensitivity reactions with clinical symptoms of allergy but without detectable immunological sensitization. The term "anaphylactoid reaction" has been proven very valuable in the clinical setting in order to make a clinical diagnosis prior to the elucidation of the pathomechanism, which often is only possible after days or weeks or, in some cases, never.

Clinical Symptomatology and Pathophysiology

The clinical symptoms of anaphylaxis represent a syndrome involving many organs. Most commonly, the reaction begins with skin involvement (pruritus, flush, urticaria, or angioedema). Prodromal paresthetic sensations on palms and soles, itching in the genital area or the pharynx, and feeling of anxiety are common. In the upper airways sneezing or rhinorrhea may precede dyspnea because of either laryngeal obstruction or bronchospasm, dysphonia, hoarseness, feeling of "tight-throat," cough, or wheezing. Respiratory involvement may lead finally to cyanosis and respiratory arrest. Frequently the gastrointestinal tract is involved, with subjective symptoms, such as nausea and cramping (uterine cramps may also occur), vomiting, diarrhea, miction, or defecation. Cardiovascular involvement may consist of early tachycardia, changes in blood pressure (sometimes an initial rise is later followed by hypotension), arrhythmia, shock, and/or cardiac arrest. A grading scale for the intensity of clinical symptoms of anaphylaxis (11) has proven valuable (Table 1). However, a variety of other signs and symptoms of not so a specific nature also occur, like sweating, headache,

Table 1
Grading of Anaphylactic/Anaphylactoid Reactions According to Severity
of Clinical Symptoms

Grade	Symptoms			
	Skin	Abdomen	Respiratory tract	Cardiovascular system
I	Pruritus Flush Urticaria Angioedema			
II	Pruritus Flush Urticaria Angioedema (not mandatory)	Nausea Cramping	Rhinorrhea Hoarseness Dyspnea	Tachycardia (>20 beats/min) RR change (>20 mmHg systolic) Arrhythmia Shock
III	Pruritus Flush Urticaria Angioedema (not mandatory)	Vomiting Defecation Diarrhea	Laryngeal edema Bronchospasm Cyanosis	
IV	Pruritus Flush Urticaria Angioedema (not mandatory)	Vomiting Defecation Diarrhea	Respiratory arrest	Cardiac arrest

Modified from Ring and Meßmer (13).

and disorientation. Despite immediate and correct therapy, fatal outcomes can occur (14).

The kinetic of the anaphylactic symptomatology develops within minutes after contact with the eliciting agent, reaching the maximum usually between 30 and 60 min. This kinetic depends on the route of contact and speed of intestinal absorption. After intravenous allergen application immediate anaphylaxis occurs within seconds!

Biphasic reaction patterns with an immediate and "late" anaphylactic reaction have been documented and may correspond to "late-phase reactions" known from the respiratory and cutaneous allergy (12,15,16).

Electrocardiographic changes, manifesting as T flattening or inversion, supraventricular arrhythmias, bundle branch blocks, and so forth, can be observed in a high percentage of patients suffering from anaphylactoid reactions during anesthesia (17). There have been reports of myocardial infarction following anaphylactoid reactions.

Autopsy studies in cases of fatal anaphylactoid reactions often show surprisingly few pathologic changes. Sometimes edematous obstruction of the airways, laryngeal edema, pulmonary hyperinflation, or pulmonary edema can be seen. In some cases eosinophilic infiltration around the bronchi is found. Swelling of liver, spleen, and intestine may also be observed (8,12,14,18,19). In cases of IgG-mediated immune-complex anaphylaxis, pulmonary hemorrhage and fibrinoid deposits have been found in the lung (12,20,21). Endoscopic examination of the gastric mucosa in food anaphylaxis can show hemorrhagic lesions (22).

The classical anaphylactic reaction is mediated by IgE antibodies on the surface of mast cells or basophil leukocytes, triggering mediator secretion after bridging with an, at least divalent, allergen (23,24). These reactions only occur in sensitized individuals, thus requiring previous contact with the antigen. Preformed and newly synthesized mediators, released from activated mast cells, comprise, among others, histamine, enzymes, proteoglycans, and eicosanoids, such as prostaglandins and leukotrienes, as well as the lipid mediator platelet activating factor (PAF) (8).

This mediator release reaction can be variable between individuals as well as within one individual over different periods of time. The term "releaseability" (25,26) is defined as the capacity of mediator-secreting cells to release preformed or newly synthesized proinflammatory mediators. Factors influencing mediator releaseability include neural influences (autonomic nervous system, neuropeptides), the cyclic nucleotide system, as well as certain cytokines, namely interleukin 3, which has been shown to "prime" mast cells and basophils in a way that they show an increased releaseability toward the same stimulus. Such interactions and priming phenomena between mediators and cytokines may partly explain the clinically often puzzling phenomenon of "summation anaphylaxis" or the fact that many patients allergic to a certain substance do not react with an equally intense anaphylactic reaction after every contact.

Apart from IgE, other antibody classes can also induce anaphylaxis. Immune-complex anaphylaxis (12,20,21,27) occurring with high titers of IgG or IgM antibodies lead to complement activation and formation of anaphylatoxins, inducing mediator release, vasodilation, and bronchoconstriction. Clinical examples of immune-complex anaphylaxis are reactions to blood or blood products, especially in IgA-deficient individuals after plasma therapy (28) and anaphylaxis in the course of serum sickness against xenogeneic proteins (29). Severe cases of dextran-induced anaphylactoid reactions are not pseudoallergic in origin but resemble immune-complex anaphylaxis (12,21,30). The elucidation of this pathophysiologic mechanism has opened the way to hapten inhibition as prophylaxis (19,27).

Table 2
Mechanisms of Pseudoallergic Anaphylactoid Reactions

Direct release of mediators (e.g., histamine)
Direct activation of complement system (bypass)
Interaction with kallikrein-kinin system
Shift in eicosanoid metabolism toward leukotriene formation
Platelet activation
Psychoneurogenic reactions

Pseudoallergic reactions are less well understood in their pathophysiology (Table 2). Direct liberation of mediators (histamine being only one) has been described for some drugs, such as opioids, intravenous narcotics, colloid volume substitutes on gelatin basis, radiographic contrast media, and others (31–35). Similarly, the direct activation of the complement or other plasma protein systems (kallikrein-kinin) may play a role in the development of pseudoallergic anaphylactoid reactions (36).

Neuropsychogenic reflex mechanisms must also be considered, especially in reactions to local anesthetics. With regard to the psychosomatic influences on anaphylactic reactions, one always should bear in mind that stress itself has been shown to be a direct histamine releaser (13,37).

In the endphase of an anaphylactoid reaction, similar mechanisms lead to similar symptoms: Postcapillary leakage resulting from microcirculatory disturbance is the main feature with decreased flow rates (red blood cell velocity) and capillary pressure (38).

Mast-cell-dependent anaphylactoid reactions can be detected by an increase of mast cell tryptase in the serum. In some fatal cases postmortem tryptase concentrations may be the only sign of an anaphylactoid reaction (39).

Numerous studies, particularly in animal experiments, have demonstrated the essential role of mast cells and basophil leukocytes in the pathophysiology of anaphylactoid reactions. However, several differences between animal species as well as between different subpopulations of cells have to be taken into consideration (26,39–41) (Table 3).

The histamine release reaction from mast cells and basophils is not a cytolytic process; it depends on energy, calcium, and temperature, and can be inhibited by specific agents (26).

In IgE-mediated anaphylaxis the initial triggering of the mediator release is initiated by a movement of the IgE receptor within the cell membrane. This high affinity IgE receptor has been characterized at a molecular level and consists of one α , one β , and two γ chains. α

Table 3
Characteristics of Mast Cells and Basophil Leukocytes

	Connective tissue mast cells	Mucosal mast cells	Basophils
<i>Releasers</i>			
48/80	+	—	—
Anti-IgE	+	+	+
Ionophores	+	+	+
C5a	+	(±)	+
Codeine	+	—	—
Kinin	+	—	—
Substance P	+	—	—
Trypsin	+	±	+
<i>Inhibitors</i>			
Glucocorticoids	—	+	+
Cromolyn	+	±	—
Ketotifen	+	?	+
Doxantrazole	+	+	?
ETYA	+	?	+
Histamine	±	?	+
Quercetin	+	+	+

and γ chains of the high affinity receptor have also been detected on other inflammatory cells (Langerhans' cells, monocytes, eosinophils) (42), the β -subunit of the high affinity IgE receptor seems to be specific for mast cells and basophils.

Concomitant use of β blocking agents, and perhaps also angiotensin-converting enzyme inhibitors, is able to increase the intensity of the anaphylactic pathophysiology, perhaps by interfering with the β adrenergic receptor on cells and tissues or with the formation of angiotensin peptides in the counterregulation of the microcirculatory disturbance (43,44).

We have shown that patients with severe hymenoptera venom anaphylaxis reveal significantly lower angiotensin II levels in their plasma compared to normal controls (45). There was a significant inverse correlation between the level of angiotensin II and the severity of the clinical symptoms. Interestingly, during hyposensitization, the plasma angiotensin levels also normalized.

Allergens or Other Eliciting Agents

Case Report

A fifty-three year-old woman undergoing colectomy for colorectal carcinoma without previous history of atopy or allergy

recovered from surgery and received an intravenous infusion with 5% human serum albumin on day three after operation. After two minutes and only few ml of the colloid infused, the patients complains of nausea. Erythematous patches appear in the face and on the trunk. Tachycardia and hypotension develop. The patient loses consciousness. Fortunately a doctor being in the room stops the infusion (after approximately 30 ml), and replaces it by physiological saline. Blood pressure is not measurable. Peripheral pulse has disappeared, equally the carotid pulse. Auscultation reveals no cardiac sounds. Immediately introduced cardiovascular and respiratory resuscitation is successful. The patient recovers and leaves the hospital without further sequels (12).

This case report with human serum albumin as an elicitor was selected to show that there is practically no "innocent" drug in medicine that might not, in a rare case, elicit anaphylactoid reactions.

The most important elicitors of anaphylactoid reactions are listed in Table 4 and include drugs, proteins, foods, aeroallergens, additives, body fluids, latex, microbial antigens, as well as physical agents (cold, exercise, or UV irradiation) (8–10). Rare cases include passive transfer of IgE antibodies by blood transfusion, as well as an attempted suicide of a penicillin-allergic health employee (46) by taking penicillin. Factical anaphylaxis (Münchhausen's syndrome) can occur in psychosomatic or psychiatric conditions.

Regarding the epidemiology of anaphylactic reactions, little data are available on a population basis. Incidence rates of anaphylactoid reactions after application of certain drugs are better studied and show a wide variety, from 0.001 up to 10% (11)!

In the United States an estimated 100–500 fatal cases resulting from penicillin application have been estimated. Rare cases include poppy seeds, beer (hops or barley), as well as an anaphylactic reaction caused by pure ethanol (47).

Fish-allergic individuals with very high sensitization may suffer from anaphylaxis by smelling fish over a distance of more than 50 m; we have seen latex-allergic individuals who had suffered anaphylaxis after entering a beer tent where balloons had been used for decorating the ceiling! Contact anaphylaxis was reported by us after testing ointment constituents in an open epicutaneous patch test (48).

In recent years an increasing number of cases have been reported in which anaphylactic symptoms only occur after a combination of various stimuli, such as physical exercise, mental or emotional stress, acute infection, or concomitant exposure to other allergens. We refer to this phenomenon as "summation anaphylaxis" (Table 5), and believe it to be much more frequent than generally accepted. A large number of

Table 4
Elicitors of Anaphylactoid Reactions

Drugs
Foods
Additives in drugs and foods
Occupational substances (e.g., latex)
Animal venoms
Aeroallergens
Seminal fluid
Contact urticariogens
Physical agents (cold, heat, UV irradiation)
C1-inactivator deficiency
Systemic mastocytosis
Exercise
Echinococcal cyst
"Summation-anaphylaxis"
Idiopathic (?)

Table 5
"Summation Anaphylaxis"^a

Acute infection
Mental stress
Emotional stress
Physical exercise
Concomitant allergen exposure (indoor, outdoor, food)
Intake of medications (cyclo-oxygenase inhibitors, β -blocking agents)

^aDefined as the appearance of symptoms only after exposure to a combination of different allergens or influencing factors.

cases of so-called "idiopathic anaphylaxis" may fall into this group. The term "idiopathic anaphylaxis" is relative and depends on the intensity of diagnostic procedures in order to find the eliciting agent.

Diagnosis and Differential Diagnosis

The clinical symptomatology of anaphylaxis is so characteristic that generally the diagnosis of acute reaction is not difficult. However, certain differential diagnoses have to be taken into consideration (Table 6).

Table 6
Differential Diagnoses
of Anaphylactoid Reactions

Pharmacologic/toxic drug effects
Hyperventilation
Vasovagal reaction
Syncope (cardial, cerebral)
Seizure diseases
Bolus aspiration
Pulmonary embolism
Hypoglycemia
Artificial anaphylaxis (Münchhausen's syndrome)

Patients who survived an anaphylactoid reaction should be transferred to an allergy unit for allergy diagnosis. The aim of allergy diagnosis in anaphylactoid reactions is threefold:

1. Discover the eliciting agent.
2. Describe the pathomechanism involved.
3. Find a tolerable alternative.

The procedures, techniques, and principles of allergy diagnosis are based on history, skin tests, in vitro techniques, and provocation tests, and have been described in the literature (8–10,13,49,50).

In pseudoallergic reactions skin tests are generally negative. If in vitro tests are not routinely available, the cellular allergen stimulation test (CAST), measuring in vitro sulfidoleukotriene production after allergen stimulation, may be promising. In patients with a history of anaphylactoid reactions, skin and provocation tests have to be carried out under strict safety precautions and emergency conditions, preferably as an in-patient to be prepared for possible late reactions.

Prophylaxis

The most important rules for prophylaxis of anaphylactoid reactions are listed in Table 7. Allergen avoidance is the best means of prevention; however, it is only possible on the basis of allergy diagnosis and the patient must be informed about his or her condition and the nature of the eliciting agent.

When drugs with an empirically high risk of anaphylactoid reactions are indicated, so-called prophetic test procedures (allergy test

Table 7
Rules for Prophylaxis of Anaphylactoid Reactions

Correct diagnosis
Avoidance of eliciting agent
Strict indication for new drugs
"Prophetic" testing (in selected cases)
Information of the patient
Oral application of new drugs
Observation of the patient after injection
Tolerance induction (e.g., xenogeneic proteins)
Hapten inhibition (in dextran-induced anaphylaxis)
Hyposensitization (e.g., aspirin, penicillin)
Premedication with histamine H1- and H2-antagonists (e.g., radiographic contrast media, gelatin solutions, iv narcotics)

without history of prior adverse reaction) may be useful in selected cases of IgE-mediated reactions (penicillin, proteins, and so forth). After an injection a short observation of the patient is helpful to detect early anaphylactoid reactions. After oral application of the offending agent anaphylactoid reactions occur less frequently than after intravenous injection. In special cases hyposensitization with certain drugs has been tried and shown to be successful, e.g., in penicillin allergy, when penicillin was required as the antibiotic of first choice (51), or in aspirin idiosyncrasy (52). The induction of immunological tolerance against the xenogeneic protein has been shown to reduce the frequency of side reactions of antilymphocyte globulin therapy (29).

For the prevention of dextran-induced anaphylactic reactions, hapten inhibition with monovalent dextran (MW 1000; Promit) injected intravenously 5 min prior to dextran infusion has considerably reduced the frequency of side effects after dextran infusion (13,19,21,27). This principle of hapten inhibition was introduced in penicillin allergy in animal experiments; however, clinical studies have failed to introduce this as an effective prophylactic regimen in humans, mainly because of the different allergenic moieties on the penicillin molecule (53).

In pseudoallergic reactions resulting from various agents the combined application of histamine H1- and H2-antagonists has been proven successful in preventing anaphylactoid reactions (31,33,53). This holds true for intravenous radiographic contrast media, opioid analgesics, and gelatin volume substitutes.

Most important in the prevention of anaphylactoid reactions is the careful observation of the patient in the first minutes of a par-

enteral drug application. The rule is, the more severe a suspected anaphylactoid symptomatology, the earlier the symptoms will appear!

Therapy

Adequate therapy of the acute anaphylactic reaction requires fast action, calmness, clinical experience, and consideration of the severity of the symptomatology. First place an intravenous catheter and apply volume. Various schedules of treatment of anaphylaxis have been suggested according to the different levels of severity (11,54). In mild reactions (grade I), fluids and histamine H1-antagonists intravenously may be sufficient. If the reaction proceeds (and the differential diagnosis is never difficult because of the immediate progress in severity) the addition of glucocorticosteroids and epinephrine is necessary. Furthermore, depending on the organ system involved, β 2-adrenergics or theophylline may be indicated in respiratory symptoms. There is no question that epinephrine may act by prevention of mediator release, relaxation of bronchial smooth muscle in severe anaphylactoid reactions, or increase of blood pressure. However, in elderly patients with cardiac arrhythmias, ventricular fibrillation has been described (17). The application of epinephrine is no guarantee for success. In the study of Lockey et al., 18 out of 24 patients died in anaphylactic shock after immunotherapy despite having received epinephrine (55). Treatment with beta-blocking agents may complicate the situation by weakening the adrenergic action. In these patients glucagon should be given to restore the adrenoceptor density (43).

Early and sufficiently rapid volume infusion is crucial. Electrolytes and glucose may lead to edema and human serum albumin seems to disappear rapidly from the circulation; some authors therefore recommend rapid infusion of colloids like hydroxyethyl starch (1000 mL) (49).

The use of glucocorticosteroids in anaphylaxis is still controversial. Many authors believe that steroids take too long to be effective in the acute dramatic situation. However, steroids also have immediate effects on membrane stabilization and may be able to suppress the late-phase phenomena (*see above*). The evaluation of 19 cases with severe anaphylactoid reactions (grade IV, cardiac and/or respiratory arrests) after infusion of dextran solution showed a clear trend toward significant benefit from immediate high-dose glucocorticosteroid treatment (12,13). In some patients empirical evidence exists for a possible benefit for combined H1- and H2-histamine antagonist treatment of acute reactions.

In grade IV reaction immediate and adequate resuscitation can be life saving (*see above*). In addition to the classical rule of A-B-C for

general resuscitation an additional rule of A-A-C (12) (antigen off, adrenalin, cortisone) is helpful. The basis for adequate therapy is the existence of the correct emergency equipment and repeated training of the personnel. However, it has to be stated that fatal outcomes can occur, even under the best possible conditions and therapeutic maneuvers in excellent and well-equipped offices and hospitals.

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