Review

Anaphylaxis: the "killer allergy"

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Journal of the Ceylon College of Physicians, 2016, **47**, 36-43

Introduction

Anaphylaxis is an acute and potentially fatal, generalized or systemic hypersensitivity reaction that occurs, minutes or a few hours after exposure to a provoking agent.[1-4] Food items, medications and insect stings are the most frequent aetiological factors[1-4] but any substance capable of inducing systemic degranulation of mast cells and basophils can cause anaphylaxis. Therefore, anaphylaxis can occur in any clinical setting, and all health care professionals should be able to recognize and treat anaphylaxis promptly and appropriately.

In spite of international[1-4] and national[5] guidelines, clinical experience suggests that anaphylaxis continues to be poorly managed in the country, and adrenaline is not considered as the first choice in initial management in many instances. Concerted efforts are underway to improve the management of anaphylaxis in Sri Lanka, and the Ceylon College of Physicians has taken the lead in that with regular training programmes in various parts of the country.

Pathophysiology of anaphylaxis

The signs and symptoms of anaphylaxis is a result of sudden massive degranulation of mast cells and basophils. Both "immunologic" (antibody mediated, IgE being the most important) and "non-immunologic" (not mediated by antibodies) mechanisms can trigger the above reaction. There is a release of preformed inflammatory mediators such as histamine, tryptase and platelet activating factor, which in turn exerts direct effects as well as activate inflammatory pathways.

Several co-factors that increase the likelihood of developing anaphylaxis upon exposure to a trigger, have been identified. They include exercise, concomitant ingestion of alcohol, intercurrent infections, fever, emotional stress, travel or other disruption of routine, and premenstrual status in females.[1]

There are three recognized temporal patterns of anaphylaxis: uniphasic, biphasic, and protracted.[1,6]

Uniphasic anaphylaxis – Uniphasic anaphylaxis is the most common type. A uniphasic response usually peaks within 30 minutes to one hour after onset of symptoms and resolves either spontaneously or with treatment within the next 30 minutes to one hour.

Protracted anaphylaxis – Protracted anaphylaxis lasts hours to days without complete resolution of symptoms. The exact frequency of protracted anaphylaxis is unknown. It appears to be uncommon. The literature consists only of case reports.

Biphasic anaphylaxis – Biphasic anaphylaxis is defined as recurrence of features of anaphylaxis within 1-72 hours after the initial symptoms have resolved, despite no further exposure to the trigger. It usually occurs within 8-10 hours of the initial phase. It has a reported incidence around 20%.[7]

Diagnosis of anaphylaxis

The key to diagnosis of anaphylaxis involves pattern recognition.The onset of anaphylaxis is acute (usually within 2 hours of exposure to the allergen) and the progression is rapid. Typically, symptoms and signs occur in two or more body systems that include the cardiovascular system, respiratory system, gastrointestinal system and the skin and mucus membranes.[1,2,4] This cardinal feature of involvement of more than one system helps to differentiate life-threatening anaphylaxis from allergy which lies at the other end of the spectrum of hypersensitivity reactions. However, in certain circumstances, anaphylaxis can be diagnosed even with the involvement of only one body system; for example when a patient develops hypotension following exposure to a known allergen for that particular patient, presence of hypotension alone is adequate to make a diagnosis of anaphylaxis.[1]

The diagnosis of anaphylaxis can be difficult. The clinical features of anaphylaxis are non-specific (i.e. other illnesses can produce the same features), and

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anaphylaxis can present with or without a history of an exposure to a potential allergen and with or without apast history of allergy. Furthermore, it is not possible to get supportive evidence from investigations as the diagnosis of anaphylaxis need to be made promptly. Therefore, the diagnosis of anaphylaxis is based on a set of criteria applicable to different circumstances [guideline recommendations from World Allergy Organization (WAO), American Academy of Allergy, Asthma and Immunology (AAAAI), American College of Allergy, Asthma and Immunology (ACAAI),and European Academy of Allergy and Clinical Immunology (EAACI)].[1,2,4,8] These criteria have demonstrated excellent sensitivity (96.7%) and good specificity (82.4%).[4] Table 1 elaborates these criteria in a simplified manner.

Table1. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

1. *In a patient with/ without a history of allergy and with/ without exposure to an allergen*	2. *In a patient with exposure to a likely allergen for that patient*	3. *In a patient with exposure to a known allergen for that patient*
Acute onset of an illness with, • Involvement of the skin, mucosal tissue, or both[a] AND at least ONE of the following • Respiratory compromise[b] • Reduced blood pressure or associated symptoms[c]	Acute onset of an illness with any TWO or MORE of the following • Involvement of the skin, mucosal tissue, or both[a] • Respiratory compromise[b] • Reduced blood pressure or associated symptoms[c] • Persistent gastrointestinal symptoms[d]	Acute onset of an illness with, • Reduced blood pressure alone[c] OR any TWO or MORE of the following • Involvement of the skin, mucosal tissue, or both[a] • Respiratory compromise[b] • Reduced blood pressure or associated symptoms[c] • Persistent astrointestinal symptoms[d]

[a]Involvement of the skin and mucosal tissue
- generalized urticaria, itching or flushing
- swollen lips,tongue,uvula
- itching of lips, tongue, palate
- angio-oedema
- periorbital itching, erythema and oedema, conjunctival erythema, tearing
- itching of genitalia, palms, and soles
- nasal itching, congestion, rhinorrhea, sneezing

[b]Respiratory compromise
- dyspnoea, wheezing, stridor, hypoxemia

[c]Reduced blood pressure or associated symptoms
- syncope, collapse
- in adults: systolic blood pressure of <90 mm Hg or >30% decrease from his/her baseline
- in children: age specific systolic blood pressure values (<70 mm Hg from 1 month - 1 year, < 70 mm Hg + [2x age]) from 1-10 years, <90 mm Hg from 11-17 years) or >30% decrease from baseline

[d]Persistent gastrointestinal symptoms
- crampy abdominal pain, vomiting, diarrhea

Pitfalls in diagnosis

Diagnosis of anaphylaxis could be challenging in certain situations.

- Some patients with anaphylaxis have neither a history of allergy nor a history of exposure to a potential allergen. The trigger is not identified in up to 20% among those who develop anaphylaxis.[4]
- Skin and mucus membrane involvement which is considered to be typical in hypersensitivity reactions could be absent in up to 16-20% of patients with anaphylaxis.[1,9] Therefore, it is important to appreciate that absence of skin or mucus membrane symptoms/signs does not exclude anaphylaxis.
- Anaphylaxis can occur without hypotension. Cardiovascular system involvement is reported only in up to 45-72% of patients with anaphylaxis.[1,9] Waiting till hypotension develops to make a diagnosis of anaphylaxis can lead to an unnecessary delay in treatment and death.
- Anaphylaxis presents with a wide range of commonly encountered clinical features for which there could be a number of other differential diagnoses. Hence it could be easily overlooked, especially in patients with other co-morbid conditions. Adhering to the clinical criteria for diagnosing anaphylaxis helps to overcome these difficulties.

While the diagnosis of anaphylaxis is essentially clinical, measurement of serum tryptase may be useful in the subsequent confirmation of anaphylaxis in diagnostically challenging cases. However these tests are not universally available, cannot be performed on an emergency basis and are not specific for anaphylaxis.[1] Furthermore normal levels of tryptase do not rule out the clinical diagnosis of anaphylaxis. Serial measurement of tryptase levels during an anaphylactic episode, is more useful than measurement at only one point in time.

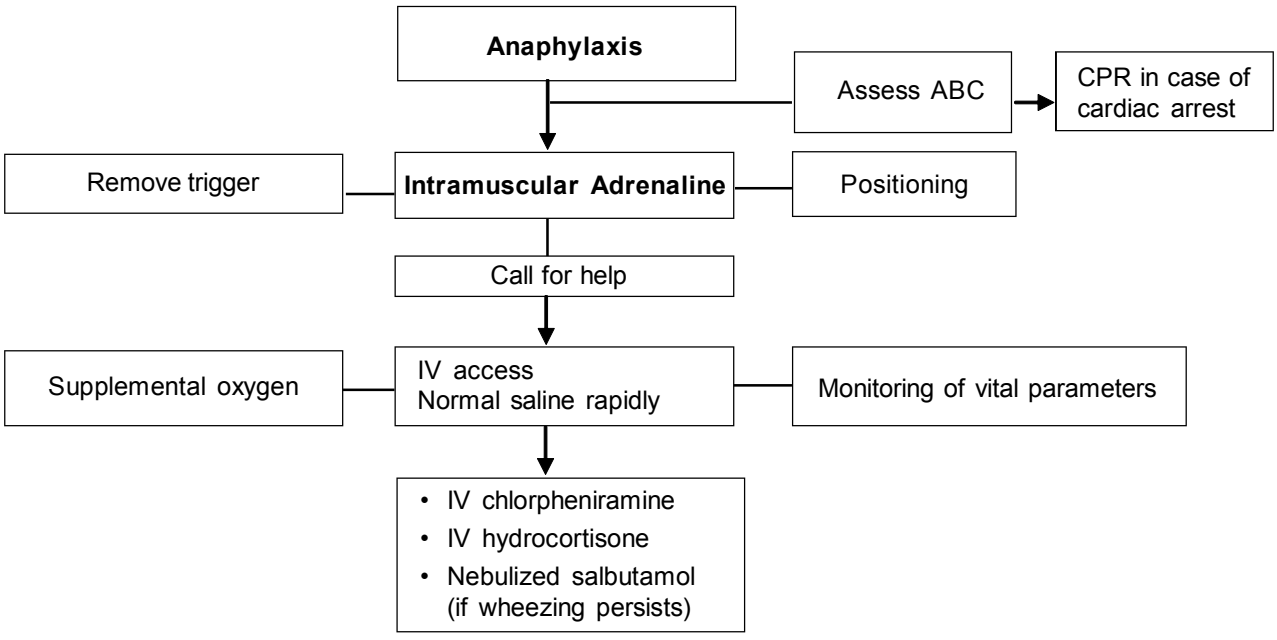
Management of anaphylaxis

Anaphylaxis is a medical emergency. Prompt assessment and treatment is essential to reduce-mortality and morbidity.

The current recommendations in international guidelines are based on best available evidence. Adrenaline and other modalities of treatment used in the management of anaphylaxis were introduced before the era of evidence-based medicine, and none of them have evidence from good quality randomized controlled trials to support their use.[10-14] However,the evidence base for adrenaline injection is stronger than for the other medications.[10,13-17] Due to obvious ethical considerations, it is unlikely that more evidence will be generated from randomized clinical trials regarding the use of adrenaline in the treatment of anaphylaxis.

The immediate management of anaphylaxis is illustrated in figure 1.

Figure 1. Immediate management of anaphylaxis



Adrenaline is the first line treatment in, anaphylaxis. As soon as anaphylaxis is diagnosed or strongly suspected, adrenaline should be administered intramuscularly.[1-4] The other measures include removal of exposure to the trigger if possible (eg. discontinuation of an intravenously administered drug), positioning the patient on the back, calling for help, gaining intravenous access, fluid resuscitation, supplemental oxygen, and continuous monitoring of vital parameters. Cardiopulmonary resuscitation should be initiated promptly in case of cardiac arrest.

Glucocorticoids, antihistamines and nebulization with beta-2 adrenergic agonists comprise second line or supportive therapy in anaphylaxis.

Adrenaline intramuscular dose

Adults

0.5 mg IM (0.5 mL of 1:1000)

Children

> 12 years: 0.5 mg IM (0.5 mL of 1:1000) i.e. same as adult dose if estimated body weight is ≥ 50kg;
0.3 mgIM (0.3 mL of 1:1000) if child is small or pre-pubertal

6 - 12 years: 0.3 mg IM (0.3 mL of 1:1000)

< 6 years: 0.01 mg/kg IM (0.01 mL/kg of 1:1000) dose to be calculated based on estimated body weight

Adrenaline

Adrenalineis the life-saving drug in anaphylaxis. It is a non-selective alpha and beta receptor agonist. Its alpha-1 adrenergic effects cause vasoconstriction in most body organ systems (except the vessels in skeletal muscles and the coronary arteries), which relieves hypotension and shock. Alpha-1 adrenergic effects also help relieve airway obstruction caused by mucosal edema. Beta-1 agonist effects result in positive inotropic and chronotropic effects that help to reverse hypotension. Beta-2 adrenergic effects relieve bronchoconstriction and in addition lead to mast cell stabilization which in turn decrease further release of inflammatory mediators primarily responsible for the pathogenesis (such as histamine and leukotrienes).

Adrenaline dosing and route of administration

In the initial treatment of anaphylaxis, adrenaline should be injected by the intramuscular route to the mid-anterolateral thigh, in a dose of 0.01 mg/kg of a 1:1000 (1 mg/mL) solution, upto a maximum of 0.5 mg in adults and 0.3 mgin children. Depending on the response, the same dose can be repeated every 5 minutes, as required.[1-4] Most patients respond to 1 or 2 doses of intramuscular adrenaline provided the initial dose is administered without delay.

The intramuscular route is preferred for initial management because intramuscular adrenaline is rapidly bioavailable and has a much better safety profile than intravenous adrenaline.[1,14,18]

Intravenous adrenaline is recommended only for patients with severe anaphylaxis refractory to intramuscular adrenaline or those who are in severe shock.[1-4] In patients with a spontaneous circulation, intravenous adrenaline can cause life-threatening hypertension, tachycardia, arrhythmias, and myocardial ischaemia. Intravenous administration of adrenaline should be done only by those experienced in its use, in a setting where patients can be carefully monitored with continuous ECG monitoring and pulse oximetry and frequent non-invasive blood pressure measurements as a minimum.[1-4] When adrenaline is administered intravenously it is essential that dilute solutions appropriate for intravenous administration (1:10,000 [0.1 mg/mL] or 1:100,000 [0.01 mg/mL]) are used. Inadvertent use of 1:1,000 (1 mg/mL) solution for intravenous administration can lead to death. Adrenaline can be given by slow intravenous injection in a dose of 50 micrograms (0.5ml of the dilute 1:10,000) in adults and 1 microgram/kg in children, repeated according to response.[3] A slow intravenous infusion need to be started for those who require multiple bolus doses.

The use of subcutaneous or inhaled adrenaline is not recommended in the treatment of anaphylaxis, due to suboptimal systemic availability of adrenaline.[3,4,18,19] However, in patients with stridor from laryngeal oedema, nebulized adrenaline can be used in addition to intramuscular adrenaline.[4]

Adverse effects of adrenaline

At therapeutic doses, adrenaline can cause transient pallor, tremor, anxiety, palpitations, dizziness and headache. Serious adverse effects such as

ventricular arrhythmias, hypertensive crisis, myocardial ischaemia and pulmonary oedema may occur after an overdose of adrenaline by any route of administration.[1] Typically, they are reported after too rapid intravenous administration or because of intravenous administration of 1:1,000 (1 mg/mL) solution instead of the dilute solutions.[20]

Adrenaline in special populations

Cardiovascular disease

Adrenaline is indicated in the treatment of anaphylaxis even in patients with concomitant cardiovascular disease, elderly and those who are at increased risk of acute cardiac events, as the benefits overweigh the risks.[1,4] However, it is important to make a correct diagnosis of anaphylaxis and to take extreme caution to avoid dosing errors.

Pregnancy

Medical management of anaphylaxis during pregnancy is not different from management of non-pregnant individuals. Adrenaline given promptly by intramuscular injection is the first-line treatment.[1] Monitoring needs to include regular fetal heart monitoring.

Infants

Extreme care should be takenin calculating and drawing up the adrenaline dose for intramuscular injection, which is 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution. Inaccuracies in dosing can lead to fatal complications.[1]

Positioning

The ideal positioning for patients with anaphylaxis is lying on the back with the lower extremities elevated. If there is respiratory distress or vomiting, the patient should be placed in a position of comfort with the lower extremities elevated. Patients with anaphylaxis should never be allowed to sit or stand up suddenly or be placed in the upright position as that can cause death within seconds due to empty vena cava / empty ventricle syndrome.[1].

Adjunct treatments

Several other treatments (oxygen, intravenous fluids and second line medications) may be considered in the management. There is no uniformity in the guideline recommendations on these. Furthermore, it cannot be overemphasized that all these treatments should be considered only after the immediate administration of adrenaline and initial resuscitation.

Oxygen

Supplemental oxygen therapy should only be considered after administration of adrenaline as laryngeal oedema needs to be relieved for satisfactory delivery of oxygen to the lungs. According to the World Allergy Organization (WAO) recommendations, supplemental oxygen should be given to all patients with respiratory distress, those who need repeated doses of adrenaline and those who have concomitant respiratory or cardiovascular diseases.[1] However, the Resuscitation Council of United Kingdom (RCUK) and the European Academy of Allergy and Clinical Immunology (EAACI) recommend supplemental oxygen for all those diagnosed with anaphylaxis.[3,4]

Intravenous fluids

During anaphylaxis, large volumes of fluid may leak from the patient's circulation and there is accompanying vasodilation.The RCUK recommends immediate administration of intravenous fluids to all patients, provided there is intravenous access.[3] The WAO and EAACI recommendation is to administer intravenous fluids to those with cardiovascular instability.[1,4] Rapid infusion of 0.9% saline or Hartmann's solution (eg. 5-10 mL/kg in the first 5-10 minutes to an adult; 10 mL/kg to a child) should be commenced.[1] The rate of administration should be titrated according to the blood pressure, heart rate and urine output and the patients should be regularly monitored for volume overload. There is no evidence to support the use of colloids over crystalloids.[1-4,21] Colloids are a recognized cause of anaphylaxis.

Second-line medications

The second-line medications play only a supportive role and do not relieve the immediately life-threatening complications of anaphylaxis such as hypotension and upper airway obstruction.

Antihistamines

Although H1-antihistamines relieve mucocutaneous symptoms, there is no evidence of their efficacy in improving outcomes in anaphylaxis.[11] When used alone, they are not lifesaving and thus should not be substitutes for adrenaline.[1-4] Their use and dosing in anaphylaxis are extrapolated from treatment of urticaria. Only first-generation H1-antihistamines (eg. chlorpheniramine) are available for parenteral use. There are concerns regarding first-generation H1-antihistamines such as worsening of hypotension with rapid intravenous administration and potentially harmful central nervous system effects (somnolence, impaired cognitive function, etc).[1-4]

Glucocorticoids

Glucocorticoids have anti-inflammatory properties. However, the onset of action of systemic glucocorticoids takes several hours and thus they are not life-saving in the initial hours of anaphylaxis. Although they have the potential to relieve symptoms of protracted anaphylaxis and to prevent biphasic anaphylaxis, a Cochrane systematic review failed to identify any evidence to confirm the effectiveness of glucocorticoids in the treatment of anaphylaxis.[12] Extrapolating from its use in acute asthma, intravenous hydrocortisone is recommended as a second line medication in anaphylaxis.[1-4]

Beta-2 adrenergic agonists

Selective beta-2 adrenergic agonists such as salbutamol may play a secondary role in anaphylaxis as supportive treatment for wheezing, cough and breathlessness due to bronchospasm not relieved by adrenaline.[1-3] However, these drugs do not prevent or relieve respiratory distress due to laryngeal oedema and upper airway obstruction. The optimal route to administer salbutamol is nebulization.

Treatment of refractory anaphylaxis

A minority of patients with anaphylaxis do not respond to timely and appropriately administered initial treatment.[1] That is refractory anaphylaxis. However, there is a multitude of reasons for an apparent lack of response to intramuscular adrenaline (Table 3). These should be looked for and corrected if possible.

Table 3. Reasons for an apparent lack of response to intramuscular adrenaline

- Adrenaline injected too late
- Patient suddenly stands or sits or is placed in the upright position after adrenaline injection
- Injection site is not optimal
- Needle is too short eg. insulin needle
- Not enough injection force used
- Adrenaline dose too low on mg/kg basis
- Adrenaline is past expiry date or inactivated due to exposure to light / heat
- Patient taking a beta-adrenergic blocker which interferes with effect of adrenaline
- Error in diagnosis

Patients with refractory anaphylaxis need management by a team of personnel experienced in safe administration of intravenous vasopressors, in a setting where adequate cardiorespiratory monitoring can be done.[1-4] Skills and facilities for airway management and mechanical ventilation are also needed.

Intravenous vasopressors and other medications

Patients with hypotension or shock refractory to initial treatment require intravenous adrenaline. Some patients may need additional intravenous vasopressor agents.[1-3] Evidence does not show a superiority among the vasopressor agents dopamine, dobutamine, noradrenaline or vasopressin (either added to adrenaline or alone).[22] In refractory anaphylaxis, adrenaline and all vasopressors need to be administered through an infusion pump and continuous monitoring of vital parameters is required to guide dose titration. When these recommendations are not followed, potentially fatal dosing errors can occur, leading to ventricular arrhythmias, hypertensive crisis, myocardial ischaemia and pulmonary edema.

Glucagon, which has non-catecholamine dependent inotropic and chronotropic cardiac effects, may be useful in patients taking a beta-blocker who have refractory hypotension with bradycardia. Although there is a pathophysiological rationale for this, the clinical evidence is limited to few case reports.[1,23] Similarly, ipratropium which has anticholinergic effects may help patients taking beta-blockers who have bronchospasms resistant to adrenaline.[1]

Duration of monitoring in the hospital

Monitoring following complete resolution of the initial phase helps to identify biphasic anaphylaxis. Based on available evidence, there are no reliable predictors of biphasic anaphylaxis.[24] There is no uniform agreement on the duration of hospital stay after initial treatment[1,2,4] but in-hospital monitoring for a minimum duration of 24 hours is advisable. In those with protracted uniphasic anaphylaxis, prolonged monitoring and interventions which can last for several days is required.

Management after discharge

Patients discharged after anaphylaxis treatment, should have a short term and long term management plan. They need to be educated about all aspects of further management.

Clear instructions need to be provided about what needs to be done in case of a recurrence that might occur during the same episode (a biphasic reaction) or later. Providing a proper diagnosis card clearly mentioning the diagnosis of anaphylaxis and the likely trigger (if identified) and providing an anaphylaxis alert card are important in the long term management. All patients diagnosed with anaphylaxis need follow-up

visits with a physician, preferably an allergy/immunology specialist, to confirm their specific anaphylaxis trigger/s, to receive immunomodulation if relevant, and to educate them to self-manage any future episodes.[1-4] Anaphylaxis trigger/s for an individual should be identified by obtaining a detailed history of the acute episode to identify the likely trigger/s, followed by allergen skin tests and/or measurement of allergen-specific IgE levels in serum to confirm sensitization to these trigger/s.

Adrenaline auto-injectors (for self-administration of intramuscular adrenaline) are useful in the self-treatment of anaphylaxis in the community.[1-4] Currently two doses are available (0.15mg and 0.3mg).0.3mg dose is appropriate for patients weighing more than 25-30kg and 0.15mg dose is appropriate for those weighing between 7.5-25kg.[4] Each patient should be prescribed two auto-injectors. The patients or the carers should be clearly educated on why, when, and how to auto-inject adrenaline. A personalized written anaphylaxis emergency action plan is useful to help them to recognize anaphylaxis symptoms, and to inject adrenaline promptly and then to seek medical assistance. Currently available adrenaline auto-injectors have some limitations that include the lack of an optimal range of doses for use in infants and young children, uncertainties about appropriate needle length for obese or overweight patients, limited shelf-life of only 12-18 months, and cost.[1,2,4]

Key summary points

- Anaphylaxis is a killer. Early detection and treatment saves lives.
- Anaphylaxis must be considered as a differential diagnosis for any acute-onset respiratory distress, bronchospasm, hypotension or cardiac arrest.
- Anaphylaxis is a clinical diagnosis; the criteria recommended by the World Allergy Organization are useful to make the diagnosis.
- As anaphylaxis is a systemic hypersensitivity reaction, it typically involves two or more systems in the body.
- Absence of skin / mucosal symptoms does not exclude anaphylaxis.
- Absence of hypotension does not exclude anaphylaxis.
- Prompt administration of intramuscular adrenaline is the mainstay in treatment of anaphylaxis.
- Additional therapy, such as supplemental oxygen, intravenous fluids, antihistamines, and glucocorticoids should not delay the administration of adrenaline.
- Intravenous adrenaline should be given only by those experienced in its use, in a setting where patients can be carefully monitored; when adrenaline is administered intravenously it is essential that appropriately diluted solutions are used.
- A proper plan of management after discharge from hospital is needed to minimize morbidity and mortality due to recurrences.

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