

Drug-Induced Anaphylaxis



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KEYWORDS

- Anaphylaxis • Drug allergy • Adverse drug reactions • Hypersensitivity
- Nonsteroidal anti-inflammatory drugs • Epinephrine

KEY POINTS

- Drugs are among the main triggers of anaphylaxis.
- Diagnosis of the causative agent is difficult, and includes clinical history and in vitro and in vivo tests.
- Skin tests are useful only for IgE-mediated anaphylaxis.
- Drug challenge is indicated in doubtful clinical history and to provide safe drug options.
- Rapid desensitization is indicated in selected cases when no cost-effective option is available.

INTRODUCTION

Hypersensitivity reactions (HSRs) induced by drugs are a subgroup of adverse drug reactions that are unexpected and characterized by objectively reproducible symptoms or signs initiated by exposure to a drug at a dose tolerated by normal individuals.¹ As defined by the International Consensus on Drug Allergy, immediate HSRs, which occur within the first few hours after drug exposure, are characterized by urticaria, angioedema, rhinoconjunctivitis, bronchospasm, and anaphylaxis.² Anaphylaxis is defined as a serious, generalized, or systemic HSR that can be life-threatening or fatal.³

Along with food and hymenoptera venom allergy, drugs are among the leading causes of anaphylaxis, particularly in adults.^{4,5} HSRs to drugs are a serious public health problem in inpatient and outpatient settings, because of high morbidity and socioeconomic costs, and they are potentially fatal.⁴

In accordance with international guidelines, the diagnosis of anaphylaxis is based on clinical findings (**Box 1**).⁶ It relies on recognition of characteristic signs and

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Box 1**Clinical criteria for the diagnosis of anaphylaxis**

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

1. Acute onset of an illness with skin-mucosal involvement and at least one of the following:
 - A. Respiratory compromise
 - B. Decreased blood pressure, syncope, or collapse OR
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient
 - A. Skin-mucosal involvement
 - B. Respiratory compromise
 - C. Decreased blood pressure, syncope, or collapse
 - D. Gastrointestinal symptoms OR
3. Decreased blood pressure after exposure to a known allergen for that patient

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symptoms, which occur minutes to a few hours after exposure to a known or potential trigger, often presenting rapid progression.

The target organs involved are variable. Typically, symptoms occur in two or more body systems: skin and mucosa, upper and lower respiratory tract, gastrointestinal tract, cardiovascular system, and central nervous system. In certain circumstances, anaphylaxis is diagnosed when only one body system is involved (eg, after an insect sting, sudden onset of cardiovascular symptoms may be the only manifestation). Skin manifestations are present in 80% to 90% of all patients, and anaphylaxis is harder to recognize when they are absent. The pattern of symptoms and signs differ from one patient to another, and even in the same patient from one anaphylactic reaction to another. At the beginning of an episode, it is difficult to predict the rate of progression or the ultimate severity.⁶⁻⁸ Misdiagnosis or overdiagnosis of anaphylaxis can occur, as described in patients with acute multisystem symptoms after ingestion of caustic substances, foreign body inhalation, acute urticaria, or angioedema.⁶

Anaphylaxis is a common manifestation in patients with systemic mastocytosis, particularly in adults with indolent systemic mastocytosis without skin involvement. Systemic mastocytosis is a disorder characterized by the abnormal proliferation and accumulation of clonal mast cells in tissues, generally harboring the KIT D816 V mutation and showing aberrant CD25 expression, accompanied by increased baseline tryptase levels.⁹ It is well defined that patients with hymenoptera venom-induced anaphylaxis who present severe reactions, including hypotension, are at high risk of having systemic mastocytosis, but this is not so clear in the case of drug reactions.¹⁰ To exclude mastocytosis, patients presenting a drug-induced anaphylactic reaction should undergo measurement of basal serum tryptase.¹⁰

EPIDEMIOLOGY

The prevalence of anaphylaxis is not well known, with an estimated overall incidence that ranges from 3 to 50 per 100,000 person-years, with a lifetime prevalence of 0.05% to 2%.¹¹ Incidence and mortality associated with anaphylaxis have been increasing, possibly because of food and drug allergy, respectively.¹²⁻¹⁴ The main causes of anaphylaxis in epidemiologic studies are drugs, food, and hymenoptera venom.⁶ Furthermore, excluding pediatric cohorts (wherein foods are

the most common trigger), medications are the most frequent cause of fatal anaphylaxis in reports from the United States, United Kingdom, Australia, and New Zealand.¹⁵

Epidemiologic studies regarding drug-induced anaphylaxis (DIA) have increased in the last 5 years. Until 2005, few studies evaluated drugs as triggers of systemic HSRs. Classes of drugs most commonly cited as triggers of anaphylaxis were antibiotics, mainly β -lactams; dextrans; radioiodinated contrast media; allergen extracts; and analgesics, particularly diclofenac.^{16–18} However, the rate of anaphylaxis induced by different classes of drugs is widely variable around the world.

Since 2013, new studies, with different methodologic designs, showed different results regarding culprit medications in DIA.^{4,19–26} Two of them, performed in France and Portugal, observed that antibiotics are still the main cause of DIA, followed by anesthesia agents, nonsteroidal anti-inflammatory drugs (NSAIDs), radio-contrast media, vaccines, immunotherapy, and chemotherapeutic and biologic agents.^{20,21} However, some other case series reported NSAIDs as the major cause of DIA, particularly in Latin American populations.^{4,19,21–23} Finally, a recent study from Korea assessing in-hospital DIA showed that platinum compounds are a major causative agent.²⁶

Several factors may explain such discrepancies between different populations. First, anaphylaxis definition and methods differ between the case series. In the Taiwan study, for example, International Classification of Diseases-9 was used to define anaphylaxis.²⁵ However, even International Classification of Diseases-10 is inadequate and led to undernotification of anaphylaxis in epidemiologic studies.²⁷ Second, genetic background, which is associated with higher risk to develop reaction to a specific drug, varies from one population to another. Finally, drugs are used differently in distinct regions. In Latin America, particularly in Brazil, NSAIDs are used indiscriminately. Dipyrone (metamizole) is available and it has been reported to be the main cause of anaphylaxis among all NSAIDs.^{4,19,21}

In the first Portuguese casuistry based on a national pharmacovigilance system, NSAIDs were not included between the major causes of anaphylaxis.²¹ However, a second Portuguese case series was published by allergists one year later based on spontaneous notification in allergy units.⁴ In that study, NSAIDs were among the main causes of DIA, in accordance with Latin-American publications.^{4,19,22,24} Confirming the diagnosis of anaphylaxis caused by NSAIDs may be difficult if European Network for Drug Allergy (ENDA) classification of NSAID HSR is used (discussed later).²⁸ For example, many cases, particularly less severe ones, may have been lost in the French and Portuguese pharmacovigilance studies published in 2013.^{20,21}

MECHANISMS INVOLVED IN DRUG-INDUCED ANAPHYLAXIS

DIA may occur by immune-mediated (allergic, mainly IgE-dependent) and nonimmune-mediated (nonallergic) mechanisms.^{29–31} Regarding IgE-mediated reactions, most drugs have low molecular weight and are not able to directly elicit an immune response. In these cases, they act as haptens or prohaptens to become immunogenic.²⁹ However, IgG-mediated anaphylaxis was only documented in animal models.³²

Several nonimmune-mediated mechanisms of anaphylaxis have been described, such as direct degranulation of mast cell/basophil, complement activation, adenosine, and cyclooxygenase metabolism interferences, and contact system activation.³² These reactions can be clinically indistinguishable from IgE-mediated anaphylaxis. Moreover, DIA can also occur because of contaminants.²⁹ In 2007, there were about

80 deaths in the United States and Germany caused by anaphylactic reactions to heparin contaminated with oversulfated chondroitin.³³

Particularly in hypersensitivity to NSAIDs, nonallergic reactions are more frequent than IgE-mediated reactions. These idiosyncratic reactions seem to occur based on an imbalance of cyclooxygenase metabolism, with overproduction of leukotrienes and underproduction of prostaglandins.²⁸ NSAID HSR has been classified in five different endotypes/phenotypes based on mechanisms involved and clinical presentation.²⁸ Nevertheless, this classification is not able to include all patients with HSR to NSAIDs. One specific phenotype that is not cited in the ENDA classification²⁸ is the designated “blended reaction”³⁴ These reactions are “mixed” reactions, when patients have immediate skin plus respiratory symptoms induced by different classes of NSAIDs, characterizing a nonallergic anaphylaxis. In the European classification, anaphylaxis triggered by NSAIDs is mainly considered IgE-mediated. In two recent articles, these blended reactions are better discussed, and two new classification proposals are described.^{35,36}

In our experience, nonallergic HSR to NSAIDs, including anaphylaxis, is much more frequent than IgE-mediated HSR.¹⁹ However, NSAID nonallergic anaphylaxis tends to be less severe than IgE-mediated anaphylaxis. In a previous study published by our group, we showed that nonallergic NSAID-induced anaphylaxis rarely causes hypotension, and our patients had a higher frequency of urticarial, angioedema, and bronchospasm, compatible with a blended reaction. However, IgE-mediated anaphylaxis to other drugs was associated with higher rates of hospitalization, intensive care unit admission, and intubation (Table 1).¹⁹

A novel mechanism was recently proposed to explain some nonallergic (“pseudoallergic”) reactions induced by drugs. It has been recently described that basic secretagogues activate mouse mast cells in vitro and in vivo through a single receptor, the Mrgprb2, which is orthologue of the human G-protein-coupled receptor MRGPRX2.³⁷ It has been shown in mice that quinolones, neuromuscular blocking agents, and icatibant activate mast cells through Mrgprb2. Some non-IgE

Table 1 Comparison between IgE-mediated drug-induced anaphylaxis and nonallergic-induced anaphylaxis induced by nonsteroidal anti-inflammatory drugs in terms of clinical features and severity			
Total N = 77	IgE-Mediated DIA, % N = 20	NSAIDs-Induced Anaphylaxis (Nonallergic), % N = 57	P Value (Chi-Square Test)
Signs and symptoms			
Urticaria and angioedema	70	91.2	.020
Bronchospasm	65	86	.042
Hypotension	75	22.8	.001
Severity criteria			
Hospitalization	80	22.8	.001
ICU admission	50	17.5	.004
Intubation and/or tracheostomy	45	14	.004

Abbreviation: ICU, intensive care unit.
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mediated “anaphylactoid” reactions in humans triggered by quinolones and neuromuscular blocking agents could be explained by this mechanism.^{37,38}

Lastly, some drugs can act as a “cofactor” to elicit an anaphylactic reaction. The most commonly cited drugs in this category are NSAIDs. Other drugs turn mild reactions into life-threatening and treatment refractory anaphylaxis, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β -blockers.^{6,29,32}

Table 2 summarizes the main triggers of DIA, possible mechanisms involved, and possible in vitro and in vivo tests available.

Table 2 Drugs and/or agents mostly cited in case series as causes of drug-induced anaphylaxis, probable mechanisms involved, and evidence of IgE participation for allergic reactions			
Drug/Agent	Type of HSR	Evidence of IgE-Mediated Reaction	References
Antibiotics			
β -Lactams	IgE-mediated	Skin tests Serum sIgE BAT	Decuyper et al, ³⁹ 2017
Quinolones	IgE-mediated and nonallergic (mast cell degranulation through MRGPRX2 pathway?)	Serum IgE BAT	McNeil et al, ³⁷ 2015; Aranda et al, ⁴⁰ 2011
NSAIDs			
Pyrazolones	IgE-mediated and nonallergic	Skin tests BAT	Decuyper et al, ³⁹ 2017
Other groups	Nonallergic IgE-mediated?	BAT ?	Kowalski et al, ²⁸ 2011; Ayso et al, ⁴¹ 2013
Chemotherapeutic agents			
Platinum salts	IgE-mediated	Skin tests Serum sIgE BAT	Giavina-Bianchi et al, ⁴² 2017; Caiado and Castells, ⁴³ 2015; Giavina-Bianchi et al, ⁴⁴ 2017
Taxanes	IgE-mediated and nonallergic	Skin tests	Picard et al, ⁴⁵ 2016; Prieto García and Pineda de la Losa, ⁴⁶ 2010
Biologic agents	IgE-mediated, cytokine storm, or mixed reactions	Skin tests for a few agents	Galvão and Castells, ⁴⁷ 2015; Brennan et al, ⁴⁸ 2009; Picard and Galvão, ⁴⁹ 2017
Intraoperative agents			
NMBAs	IgE-mediated and nonallergic (mast cell degranulation through MRGPRX2 pathway?)	Skin tests Serum sIgE	McNeil et al, ³⁷ 2015; Decuyper et al, ³⁹ 2017
Latex	IgE-mediated	Skin tests Serum sIgE	Gaspar and Faria, ⁵⁰ 2012
Radioiodinated contrast media	IgE-mediated and nonallergic	Skin tests BAT	Decuyper et al, ³⁹ 2017

Abbreviations: BAT, basophil activation test; NMBAs, neuromuscular blocking agents; sIgE, serum-specific IgE.

DIAGNOSIS

Anaphylaxis

Physicians must be prepared and well trained to confirm the diagnosis of anaphylaxis. Diagnosis is essentially clinical and based on signs and symptoms presented during the reaction (see [Box 1](#)).⁶ Underdiagnosis is more common when there is no mucocutaneous involvement.⁶

Particularly in perioperative anaphylaxis, surgeons and anesthesiologists should be aware of this uncommon condition. There are several differential diagnoses of respiratory and cardiovascular dysfunction during surgeries, and skin involvement that is observed in more than 90% of patients with anaphylaxis may be less frequent in perioperative reactions, making the diagnosis more difficult. In addition, skin manifestations are also not easily recognized when present, because the patient is covered and sedated, being unable to report pruritus.⁵¹ Anesthesiologists should not underestimate immediate isolated skin manifestations. Although these reactions are not anaphylactic, they are considered grade I systemic reactions and they may predict a more severe reaction in a subsequent re-exposure to the culprit agent.⁵²

In systemic acute reactions after NSAID exposure, clinical diagnosis of anaphylaxis based on the current ENDA classification in five endotypes/phenotypes of reactions is difficult.²⁸ Using this classification, anaphylaxis is restricted to those IgE-mediated severe reactions induced by one group of NSAIDs in patients who tolerate other groups. These patients are considered selective responders.

However, many patients cross-intolerant to different groups of NSAIDs may present skin (urticaria/angioedema) plus respiratory compromise (rhinosinusitis and bronchospasm), in an acute basis, which is compatible with anaphylaxis.¹⁹ These blended reactions seem to be non-IgE-mediated and nonallergic, resulting from the inhibition of cyclooxygenase-1 and prominently cysteinyl leukotriene overproduction.^{28,34,53} They are frequently less severe than IgE-mediated anaphylaxis (see [Table 1](#)).¹⁹ However, clinicians should keep in mind that these reactions should be considered anaphylactic and patients must not take any NSAID until evaluation by the allergist.

Serum tryptase levels measured 30 to 180 minutes after symptoms onset may support the clinical diagnosis of anaphylaxis in some but not all patients.⁶ If possible, the test should be done after intraoperative reactions, and an elevated “acute” serum tryptase level is highly predictive of IgE-mediated reaction.⁵⁴ If a high level of tryptase is found after an anaphylactic reaction, it should be measured again within a few weeks to exclude the diagnosis of mast cell disorders. Other mediators and their metabolites are potential biomarkers and can be measured in serum and/or 24-hour urine, although most of them are not available in clinical practice. The most studied are histamine, *N*-methylhistamine, *N*-methylimidazole acetic acid, methylimidazole acetic acid, carboxypeptidase, platelet aggregation factor (PAF), prostaglandin D2 (PGD2), prostaglandin F alfa (PGFalfa), and leukotriene E4 (LTE4).

Etiologic Agent

Clinicians should initiate investigation just after the acute reaction. Detailed analysis of patient clinical history is the primary and most important tool available for diagnosis of DIA. Even if the physician has confirmed the diagnosis of DIA and has identified the culprit agent, the patient should undergo evaluation by an allergist, bringing the initial medical report. Follow-up is essential because education regarding anaphylaxis is important to prevent potential future events.²⁹

When many drugs are suspected to cause the anaphylactic reaction, a copy of the medical record, particularly in the perioperative reactions, is crucial. Then the allergist

should draw a “time line” to identify which agents should be considered as real suspects and to define the investigation algorithm. History of prior HSRs to any drug should be taken into consideration, because it is not uncommon to see patients who present severe reactions after re-exposure to unrecognized culprit drugs or to drugs with high risk of cross-reactivity or cross-intolerance.

After a detailed clinical history, *in vitro* or *in vivo* tests are used to complete the investigation. Because anaphylaxis is a typical immediate reaction, according to the mechanisms involved, investigation should concentrate on specific IgE and/or basophil and mast cell activation.

In terms of laboratory tests to diagnose the culprit agent, few options are available in clinical practice. Serum-specific IgE assays are available for few drugs and, particularly for β -lactam antibiotics, its sensitivity is low.⁶ Basophil activation tests may help in diagnosing IgE-mediated or non-IgE-mediated hypersensitivity. However, commercially available basophil activation tests do not have their accuracy established.²⁹

Thus, *in vivo* tests are the best option to help allergists to confirm or exclude different drugs as the causative agent of an HSR. Either skin and drug provocation tests (DPT) are important options to diagnose HSRs. As suggested by international guidelines, drug allergy is an HSR involving a specific immunologic mechanism.² In drug allergy, skin testing is the method most widely used to determine sensitization, because other tests are less sensitive (*in vitro* tests) and specific, or potentially harmful (DPT). When facing a potential allergic reaction, the recommendation is to perform skin tests before DPT, because they allow one to define the mechanism involved in the reaction and they are safer than DPT.² It is recommended to perform skin prick tests and, if they are negative, intradermal tests. Some of the main triggers of DIA and the indications of *in vitro* and *in vivo* tests are summarized in [Table 2](#). Although there is no international consensus on how skin tests with drugs should be performed and interpreted, there are many drugs for which nonirritating concentrations have been shown to be reliable.⁵⁵

When clinical history and skin testing are not enough to confirm the diagnosis, DPT may be recommended.² DPT is the controlled administration of a specific drug with the purpose of diagnosing HSR. They are considered the gold standard for establishing or excluding the diagnosis of hypersensitivity to a given drug. In addition to reproducing the allergic symptoms, DPTs reproduce any clinical manifestation of hypersensitivity, regardless of the mechanism involved (immune- or nonimmune-mediated).⁵⁶ However, in a patient with a likely diagnosis of DIA, drug challenge to the culprit drug should not be performed. Negative skin tests to most implicated drugs lack the negative predictive value to recommend drug challenges in the setting of a reliable history.²⁹

In DIA, allergists should keep DPT for specific situations, such as to find a safe therapeutic alternative to an implicated drug (eg, another β -lactam antibiotic for a patient with penicillin-induced anaphylaxis). In our experience, finding an alternative to the culprit drug is safe and is the major indication to perform a DPT.⁵⁷ Another indication to perform DPT is in “allergic” patients who had reactions not suggestive of anaphylaxis. In a previous review of DIA published in this journal,²⁹ Kuruvilla and Khan described that vocal cord dysfunction is an important differential diagnosis of anaphylaxis, particularly when the reaction is recurrent with many unrelated drugs. In these patients, DPT with the suspect agent is indicated in conjunction with laryngoscopy.²⁹

When a drug is excluded as the cause of an HSR, it is important to rewrite a new medical record, changing the previous status.²⁹ Obviously, if DPT was performed with an alternative drug, this report should describe the tolerance to the drug tested,

but maintaining the status of hypersensitive to the drug probably implicated in the reaction.

In Fig. 1 we propose a diagnostic algorithm for DIA.

MANAGEMENT

Anaphylactic Reaction

Anaphylaxis is a life-threatening medical emergency in which prompt intervention is critical. During an acute reaction, the patient should be placed on the back with their lower extremities elevated. Epinephrine (adrenaline) is the first-line drug to treat anaphylaxis because it is the only medication proven to reduce hospitalization and death. It should be injected by the intramuscular (IM) route in a dose of 0.01 mg/kg of a 1:1000 (1 mg/mL) solution, to a maximum of 0.5 mg in adults and 0.3 mg in children. The dose is repeated every 5 to 15 minutes, as needed.^{6,8,58}

The route of epinephrine administration for anaphylaxis should be IM, instead of subcutaneous or intravenous (IV) routes. Particularly for DIA in hospitalized patients, during intraoperative immediate HSR or while administering antibiotics, chemotherapy, or monoclonal antibodies, physicians tend to use IV adrenaline, because venous access is already available. However, there are limited data on the effective and safe dose of IV epinephrine to anaphylaxis. In a recent study, the IV route of epinephrine for anaphylaxis was associated with a higher frequency of overdoses and more adverse events, inducing 10% of cardiac ischemia.⁵⁹ In conclusion,

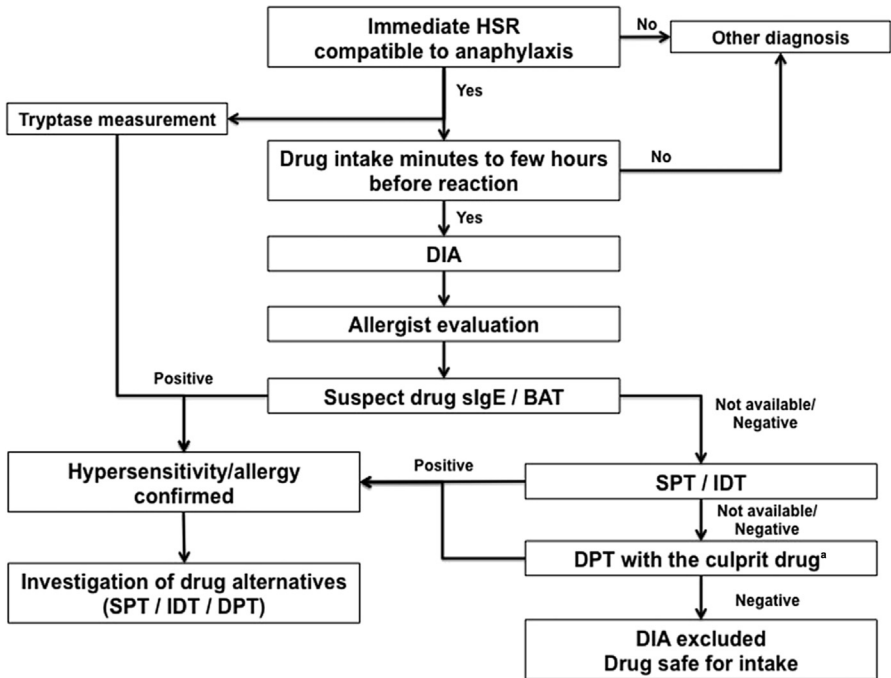


Fig. 1. Diagnostic algorithm for drug-induced anaphylaxis. ^aIndications for drug provocation test with the suspect drug include unreliable clinical history (reaction was not truly anaphylaxis), such as drug-induced vocal cord dysfunction. BAT, basophil activation test; IDT, intradermal test; sIgE, serum-specific IgE; SPT, skin prick test.

IM epinephrine, preferably applied into the thigh, is the proper route to treat anaphylaxis.⁶

Large volumes of fluids should be administered as soon as hypotension and shock are recognized.⁶⁰ Second-line medications, such as antihistamines, β_2 -adrenergic agonists, and glucocorticoids, must not delay adrenaline administration. Glucocorticoids are typically used to prevent biphasic episodes of anaphylaxis and have little or no effect on initial symptoms and signs.^{6,8}

Patients who present anaphylaxis while under treatment with β -blockers may benefit from glucagon administration. Moreover, physicians should pay special attention in patients under angiotensin-converting enzyme inhibitor treatment, because they frequently present prolonged hypotension with poor prognosis.^{6,8}

Follow-up

After the initial HSR, prevention of new episodes is crucial. Once the diagnosis of DIA has been established, the mainstay of treatment is avoidance of the drug involved and those chemically related, which could potentially lead to cross-intolerance or cross-reactivity. Patients must avoid drugs related to the culprit one until an appointment with the allergist, who will evaluate the clinical history and perform in vivo and/or in vitro testing if necessary. As soon as investigation is complete, a final medical report should be written by the allergist to allow patients and their physicians' orientation.⁶ However, even patients with clear medical reports are not totally free of a recurrent anaphylactic reaction. Epinephrine auto-injectors should be prescribed aiming to decrease morbidity and mortality associated with a future inadvertent reaction.⁶

In case of radiocontrast media hypersensitivity, patients with a history of immediate reactions should receive corticosteroid and antihistamine premedication before re-exposure. Because IgE-mediated anaphylaxis to radiocontrast media is rare, there is a universal consensus that routinely skin testing for all patients with a past reaction is not effective.⁶⁰

In some cases, there is no alternative drug to treat a patient's condition instead of the drug imputed in the HSR.⁶¹ Thus, drug desensitization is indicated as an effective approach to the management of IgE- and non-IgE-mediated HSR.⁶² Mainly for immediate HSR, rapid drug desensitization is the process of induction of a state of unresponsiveness to a drug responsible for an HSR in a short period of time, usually some hours.⁶¹ Rapid drug desensitization is a therapeutic procedure indicated for patients with proven or highly suspected HSRs after an individual risk/benefit assessment showing that the benefits outweigh the risks. In case of DIA induced by antibiotics, chemotherapeutic agents, and monoclonal antibodies, it was demonstrated that rapid drug desensitization is cost effective and safe to maintain hypersensitive patients on first-line therapy.⁶³ Rapid drug desensitization should be performed by allergists with experience in those procedures, in a hospital basis, and sometimes in intensive care settings because of the intrinsic risk of inducing a severe anaphylaxis when re-exposing patients to the causative agent.^{61,63}

SUMMARY

DIA can be life-threatening, and re-exposure to the agent involved in the initial reaction is common. However, many patients are labeled as "allergic" after unclear reactions not compatible with anaphylaxis, and avoid drugs that could be cost effective and safe. One should encourage patients and clinicians to undergo an allergist evaluation after an anaphylactic reaction, to complete investigation and to receive a conclusive medical report that helps in future drug management.

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